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ACUTE PERICARDITIS*

A Graphic Correlation of the X-Ray, Clinical and Electrocardiographic Findings

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WITHIN a period of three months, 8 cases of pericarditis were treated on the Cardiology Section of the Medical Service at the Battey General Hospital. In studying these patients, a graphic method was devised to correlate the clinical, x-ray and electrocardiographic changes. It was found that the observed alterations followed a variable sequence in different cases — variations that are incompletely described in the textbooks. Inasmuch as the diagnosis of acute pericarditis is often difficult, it is important to discuss thoroughly the variations that may be encountered. It was also noted that patients with purulent pericardial infections, when treated with penicillin and the sulfonamides, followed a different clinical course from that usually described. These cases are therefore presented to emphasize the variable sequence of x-ray, clinical and electrocardiographic findings, and also to demonstrate the relatively benign nature of certain cases of pericarditis when treated by modern methods.

THEORETICAL CONSIDERATIONS

In 1929, Scott, Feil and Katz[1] first described the RS–T elevation occurring early in a case of hemopericardium and in one of purulent pericarditis. At the same time, they[2] reported the experimental production of changes in the RS–T segment in dogs by the injection of oil or saline solutions into the pericardial sac. They attributed these changes to generalized ischemia of the myocardium produced by pressure. In 1932, Foulger and Foulger[3] showed that the electrocardiographic changes produced in such an experiment were temporary unless the intrapericardial pressure was maintained. They demonstrated that the pericardial sac soon stretched, allowing the pressure to fall and the electrocardiogram to return to normal. It was their impression that the change in the RS–T segment was an indication of recent effusion, or of effusion so gross as to prevent further stretching of the pericardial sac. In 1933, Fowler, Rathe and Smith[4] showed that the T-wave changes in experimental pericarditis could be correlated with the inflammatory reaction in the subepicardial myocardium. They also showed that when the subepicardial myocarditis had subsided and the inflamed area had been replaced by fibrous tissue, the T waves returned to normal. In 1934, Herrmann and Schwab,[5] on the basis of experimental work, observed that the early changes in the RS–T segment were due to ischemia of the myocardium, whereas the later T-wave alterations were caused by subepicardial myocarditis. In 1937, Vander Veer and Norris[6] reported autopsy findings in 10 cases of acute pericarditis. Six of these cases had shown characteristic electrocardiographic changes during the disease, and in all 6 there was definite post-mortem evidence of subepicardial myocarditis. In the 4 cases without characteristic electrocardiograms, 3 showed no involvement of the subepicardial area and 1 had minimal involvement. In 1938, Bellet and McMillan[7] made histologic studies in 19 cases of acute pericarditis. They also concluded that subepicardial myocarditis was the cause of the electrocardiographic changes. They demonstrated that elevation of the RS–T segment was an extremely transient affair and was especially likely to occur in association with rapidly developing types of pericarditis. In tuberculous pericarditis they found it to be infrequent and usually minor. One of their observations is of particular interest: "Inversion of the T wave was probably associated with the subacute or subchronic stage and occurred when the pericardial process was healing and the general toxemia was less marked." In 1939, Vander Veer and Norris[8] again discussed the electrocardiographic changes in acute pericarditis and this time included the changes seen in Lead 4R, the chest lead. They reported that the RS–T elevations were very transient, and observed that the electrocardiograms might return almost to normal even though the infection and inflammation of the pericardial sac were continuing and the pericardial effusion was increasing.

In 1940, Noth and Barnes[9] reviewed the literature up to that time and presented their findings in 53 cases, 25 of which came to autopsy. They ques-

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tioned the tamponade theory of the production of electrocardiographic changes in acute pericarditis, believing that the subepicardial myocarditis was a satisfactory explanation of the alterations. It was their impression that the most characteristic acute change in pericarditis was an elevation of the RS–T segment and an exaggeration of the T waves in the limb leads. This is followed by a return of the RS–T segments to normal, with a progressive lowering of the T waves, often proceeding to actual negativity. They did not observe elevations of the RS–T segments in tuberculous pericarditis.

As regards the electrocardiographic changes in rheumatic pericarditis, there is little in the literature. Winternitz and Langendorf[10] reported their observations in 18 cases. Inasmuch as rheumatic pericarditis has often been considered to occur as an extension of myocarditis, there should be a sequence of events different from that seen in infectious pericarditis. Winternitz and Langendorf did not find this to be true, and their cases of rheumatic origin behaved exactly like those arising from other causes. In 8 of the cases in which they were able to follow the course of the disease completely, the tracings between the fifth and thirteenth weeks went through the stage of inversion of the T wave to restitution of a normal appearance.

Material

This series includes 8 cases of acute pericarditis. Six of these patients were followed in this hospital during all or part of the acute disease, and the other 2 were transferred here for convalescent care and disposition. The patients were men between the ages of twenty-two and twenty-seven. Six were Whites and two were Negroes. There were no deaths in the series during the time under observation at this hospital.

Etiologically the causative organism was demonstrated satisfactorily in 3 cases (it was the tubercle bacillus in 1 case, a meningococcus in 1 and a pneumococcus in 1). In 5 cases, the clinical course established strong presumptive evidence as to etiology, with a probable tuberculous origin in 2 cases and a probable rheumatic one in 3.

Method of Study

A graph was devised to correlate several features. The so-called "heart size" recorded was the greatest transverse diameter, measured in centimeters on the standard 72-inch roentgenogram. The sum of the T waves in the four leads was determined algebraically and charted in millimeters. The elevations of the RS–T segment in the four leads were added and also charted in millimeters. The temperature was the highest recorded each day. The period of time that the friction rub was heard was charted. The electrocardiograms were made with the three standard limb leads and a precordial lead (Lead CF_4).

Case Reports

Case 1 (Fig. 1). This 23-year-old soldier was admitted for treatment of a traumatic amputation of the left leg. The wound was clean and almost completely healed at the time of admission. While in the hospital, on April 10, 1944, he developed left pleurisy with effusion. Six hundred and seventy-five cubic centimeters of straw-colored fluid was removed from the left pleural space on April 19. Some of this fluid was injected into a guinea pig, which developed typical generalized lesions of tuberculosis within 6 weeks. The patient

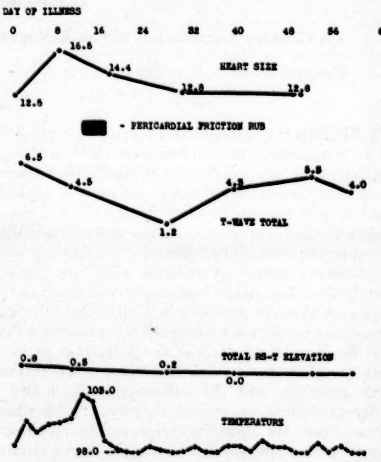


Figure 1. *Graph of Findings in Case 1.*

required no further thoracenteses and improved rapidly, becoming afebrile by May 18.

On the evening of June 8, he developed nonradiating substernal pain, which was increased by respiratory movements. The temperature rose to 101.2°F. Pericarditis was suspected, but electrocardiograms taken at that time were normal except for a slight RS–T elevation (Fig. 2*A*). On June 18, the 10th day of the pericarditis, the electrocardiograms revealed some reduction in the RS–T elevation, with a general reduction in QRS voltage in all leads. The T waves in the limb leads were of lower voltage than in previous electrocardiograms (Fig. 2*B*). X-ray films taken 2 days earlier had demonstrated an increase in the cardiac shadow, with a globular configuration suggestive of pericarditis. A to-and-fro friction rub was heard over the precordium. On July 7, the electrocardiograms showed an isoelectric T_1 and an inverted T_4. T_2 was lower than in previous electrocardiograms (Fig. 2*C*). X-ray examination on July 10 revealed a normal cardiac shadow. By July 19, the electrocardiogram showed a slightly upright T_1 and an upright T_4. T_2 and T_3 had returned to normal (Fig. 2*D*). X-ray examination of the chest on July 31 showed no change.

Case 2 (Fig. 3). On March 16, 1944, this 24-year-old soldier was admitted to a hospital overseas in a state of profound shock. He was conscious and stated that he had had fever, headache, nausea and vomiting for 24 hours. His neck was stiff. A lumbar puncture done on admission produced grossly purulent fluid containing meningococci on smear and culture. Ten thousand units of penicillin was given intrathecally, followed by 50,000 units intravenously and 50,000 intramuscularly. The patient was also given 5 gm. of sodium sulfadiazine intravenously and thereafter was carried on large doses of sulfadiazine and penicillin.

On the 3rd day of meningococcemia the patient complained for the first time of constant soreness in the neighborhood of the ensiform cartilage, accompanied by a sharp pain beneath the lower sternum on deep inspiration, occasionally radiating to the left shoulder. A loud pericardial friction rub was heard over the entire precordium. An electrocardiogram revealed elevation of ST_2, with inversion of T_3 and moderate right-axis deviation. On the 5th day of the disease, the pericardial rub was less pronounced. Ten cubic centimeters of serofibrinous fluid was removed from the pericardial sac and

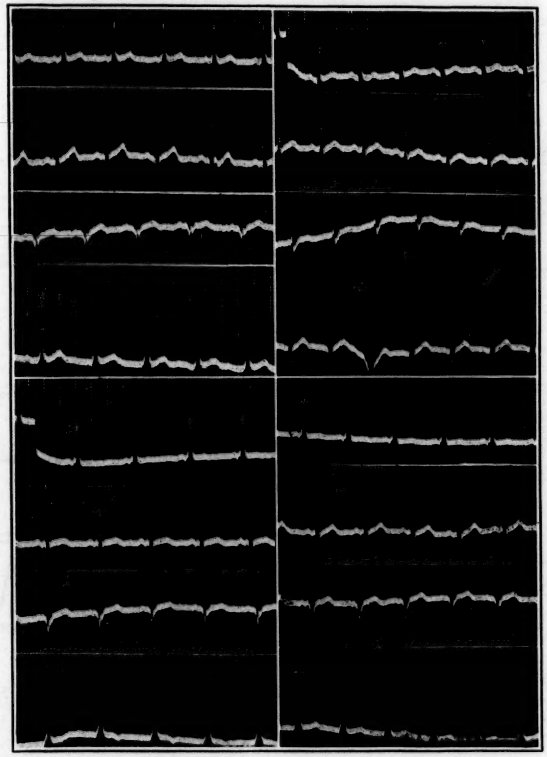


FIGURE 2. *Electrocardiograms in Case 1.*
A *was taken on the first day of disease,* B *on the tenth day,* C *on the twenty-ninth day, and* D *on the forty-first day.*

30,000 units of penicillin was instilled intrapericardially. At the same time 10 cc. of similar fluid was withdrawn from the left pleural space. The pleural fluid showed 7600 white cells per cubic centimeter, with 93 per cent polymorphonuclear cells. Culture of the fluid was sterile. The pericardial rub persisted until the 19th day. Clinical recovery was slow but uneventful. At the present time the patient is asymptomatic.

CASE 3 (Fig. 4). This 25-year-old soldier was well until May 8, 1944, when he developed fever, chills, pain in the right chest and a cough productive of blood-tinged sputum. He was hospitalized on May 12, at which time x-ray examination revealed pneumonia involving the right lower lobe. Despite adequate doses of sulfadiazine, the process spread, until it involved all three lobes on the right. Sulfonamides were stopped on May 19, at which time the patient developed right-sided pleurisy. On the following day 300 cc. of cloudy, straw-colored fluid was removed from the right pleural space. Smear and culture of this fluid showed a gram-positive diplococcus culturally similar to pneumococcus. No typing was done. On May 22, penicillin therapy was instituted, a total of 1,730,000 units being given in the next 16 days. On the same day excessive dyspnea and tachycardia were noted for the first time, and by May 25 a typical pericardial friction rub was heard over the entire precordium and persisted for 7 days. At that time, the temperature, which had been resolving by lysis, rose to 101.5°F. By June 6 it was normal, and convalescence from that point was uneventful.

Electrocardiograms made on May 24, the 2nd day after the onset of symptoms of pericarditis, showed no elevation of RS–T segments or alterations in T waves. X-ray examination revealed a moderate, diffuse enlargement of the cardiac silhouette. On May 29, the cardiac silhouette had increased

markedly in size, but the electrocardiograms were unchanged. By June 3 there was definite diminution in the size of the

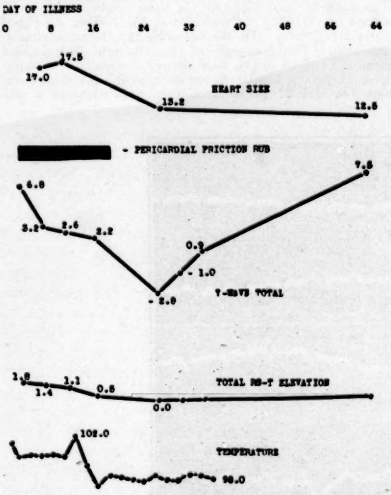


FIGURE 3. *Graph of Findings in Case 2.*

cardiac shadow but no change had occurred in the electrocardiograms. X-ray examination of the chest on June 8

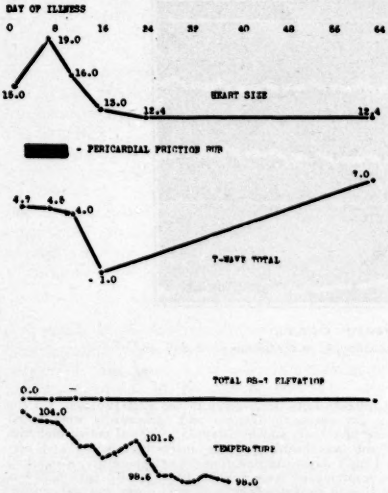


FIGURE 4. *Graph of Findings in Case 3.*

revealed reduction of the cardiac silhouette to normal. Electrocardiograms made on that day, however, showed for the first time a diphasic T_1 inverted T_2 and T_4 and an isoelectric T_3. On July 26, the 65th day of the pericarditis, both chest x-ray film and electrocardiogram were normal.

CASE 4 (Fig. 5). This 27-year-old soldier was well until December, 1943, when he developed "flu" in England. He recovered after a week and was well until March, 1944, when he had an attack of so-called "primary atypical pneumonia."

On May 8, the patient developed cough, fever and pain in the left chest, aggravated by deep breathing. The next day, beginning to raise much yellow sputum, he was put on sulfadiazine, which was continued for 5 days. On May 14, he was admitted to the hospital with a high temperature. There were rales at both lung bases, the liver was enlarged, and the neck veins were distended. On May 17, mercurial diuretics were tried, with moderate success. During that time the liver increased rapidly in size and became tender.

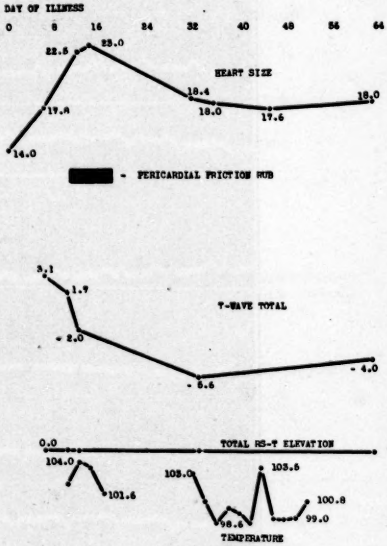


FIGURE 5. *Graph of Findings in Case 4.*

On May 19, a pericardial tap was performed and 80 cc. of clear yellow fluid was removed. The fluid formed a pellicle within a few minutes and clotted within an hour. No organisms could be demonstrated on smear or culture. After pericardiocentesis, there was relief of dyspnea and the previously observed pulsus paradoxicus disappeared. On May 20, a pericardial friction rub was heard for the first time, persisting until May 26. During the next month treatment consisted of bed rest and salicylates, which reduced the fever somewhat. There was at no time any evidence of joint involvement. On July 18, the condition was unchanged except for pain in the right chest and a friction rub over this area. During the next week friction rubs were heard over both pleural areas. Chest x-ray films revealed extensive pleural thickening but no free fluid.

On May 14, a chest x-ray film revealed moderate enlargement of the heart, but the electrocardiogram was normal (Fig. 6*A*). By May 20, roentgenograms showed a marked increase in the size of the heart and electrocardiograms showed slight inversion of T_1, T_2 and T_4, with a diphasic T_3 (Fig. 6*B*). On June 13, the heart had decreased in size but the T-wave inversion had increased (Fig. 6*C*). On July 10, the 63rd day of the disease, the total T wave inversion had

decreased slightly (Fig. 6*D*), but the cardiac silhouette was unchanged. Electrocardiograms made on the 86th, 89th and 93rd days of disease showed no essential change in the T wave, and the x-ray films were likewise unchanged. The patient was still running a low-grade fever and was discharged to a Veterans' Facility for further care.

CASE 5. This 24-year-old soldier was well until June 15, 1943, at which time he was admitted to a hospital overseas with complaints of fever, substernal pain, tachycardia and generalized aching. Electrocardiograms were not available, but he had no pericardial friction rub, and chest x-ray films showed no enlargement of the cardiac silhouette. He continued to have an elevated temperature for a month, but did not have true migrating polyarticular disease. The tachycardia recurred at times, and on one occasion a diagnosis of paroxysmal tachycardia was made. He was finally released from this hospital on September 20, but was readmitted on October 27 with complaints of substernal distress and dyspnea. Again the physical and laboratory studies were negative, but no electrocardiograms were taken. He was discharged on November 9.

Three days later he developed fever, with a hacking cough, substernal pain and chills. He was readmitted on November 15 with fever, leukocytosis and severe anterior chest pain. On November 18, a chest x-ray film revealed marked increase in the cardiac silhouette, and the pericardial friction rub was heard in the 4th left interspace. The patient was transferred to another hospital on November 25, the 13th day of symptoms referable to pericarditis, where electrocardiograms showed inversion of the T waves in all leads. A chest x-ray film showed no change. On December 1, the electrocardiogram was unchanged, but by December 6 there was considerable increase in negative deflection of all T waves, with an ST pattern in Leads 1 and 2 suggesting a so-called "coronary T." At that time x-ray examination showed marked reduction in the size of the cardiac shadow. On January 13, the 62nd day of disease, the heart was still smaller and the T waves were not so deep. By February 8 the heart was of normal size, but the T waves had not changed except that T_1 had become diphasic. On March 22 T_3 was upright, and the other T waves were diphasic. On June 16, the cardiac silhouette was still normal, and T_2 was normal, T_1 low but upright, and T_3 and T_4 slightly inverted. The

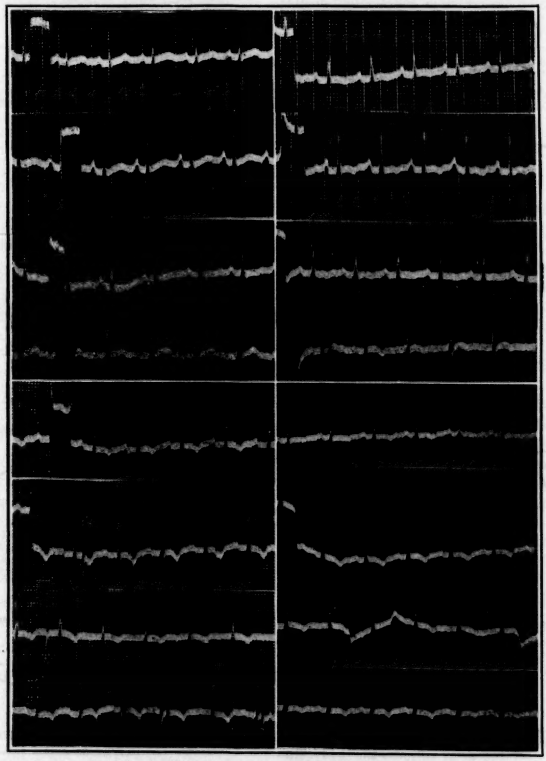


FIGURE 6. *Electrocardiograms in Case 4.*
A *was taken on the sixth day of disease,* B *on the twelfth day,* C *on the thirty-sixth day and* D *on the sixty-third day.*

patient continued to have an elevated temperature, with daily peaks of 99.8 to 100.4°F., for another month. (Progress was not recorded graphically because none of the overseas x-ray films were obtainable.)

At the time of discharge, over 9 months after onset, he was still running a low-grade fever, with low total T wave deflection, and was transferred to a Veterans' Facility for further care.

CASE 6 (Fig. 7). This 22-year-old soldier had a severe renal reaction following the giving of sulfathiazole in May, 1942, for treatment of a local infection in the right hand following an injury. He was well following this until April 24, 1944, at which time he developed a sore throat, followed within 48 hours by severe aching pain in the legs. He was treated with large doses of intravenous sodium sulfadiazine, and within 24 hours had developed grossly bloody urine and a temperature of 105.6°F. The sulfonamide was discontinued, but the patient continued to run a septic fever, with peaks over 104.0°F. daily. The white-cell count ranged between 8600 and 11,950, and all studies, including blood cultures, agglutination tests, stool and urine cultures and x-ray films of the chest, were normal.

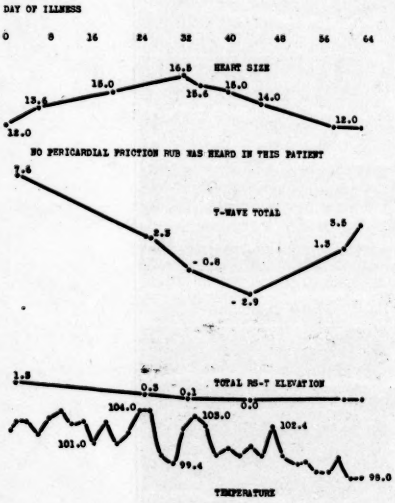
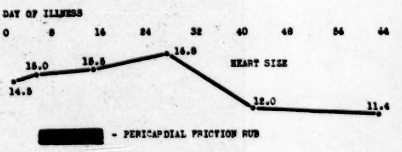

DAY OF ILLNESS
0 8 16 24 32 40 48 56 64
HEART SIZE
NO PERICARDIAL FRICTION RUB WAS HEARD IN THIS PATIENT
T-WAVE TOTAL
TOTAL RS-T ELEVATION
TEMPERATURE

FIGURE 7. *Graph of Findings in Case 6.*

On May 6, the patient complained of severe pain in the precordium. An electrocardiogram on May 8 showed an elevated RS–T segment in Leads 1 and 2 without T wave changes. X-ray examination on May 16, the 10th day of symptoms referable to the pericardium, showed no increase in the size of the heart. No electrocardiograms were available from May 8 until May 31, when the T waves in Lead 4 were inverted and those in the limb leads were lower than before but still upright. On June 8, x-ray examination revealed a marked increase in the size of the heart. An electrocardiogram on that date showed little further change, except for slightly lower T waves in the limb leads. On June 12, there was no change in the electrocardiogram or x-ray film. During that time the patient had shifting joint pains without marked swelling and a spiking fever, with the peaks less high than at admission. He had several severe chills, followed by an increase in temperature. On May 9, he had pain in the left side of the chest and a definite pleural friction rub was heard, but fluid did not appear. Six hundred and ninety thousand units of penicillin was given, without relief, but salicylates were not tried. Studies continued to be negative except for the chest x-ray film and electrocardiogram and an increased white-cell count, which reached 35,150 on one occasion, with 85 per cent polymorphonuclear cells. On transfer to this hospital on June 20, the cardiac silhouette was still enlarged and the electrocardiogram showed inversion of T waves in all four leads. The patient complained of severe joint distress without marked swelling, but had no pleural or pericardial friction rubs. The temperature was still high, but subsided within 48 hours after the patient began to receive 4 gm. of aspirin daily. On July 11, a chest x-ray film revealed a normal-sized heart. Electrocardiograms showed upright T waves in all leads.

CASE 7 (Fig. 8). This 26-year-old soldier was well until May 26, 1944, when he first noticed stiffness of the joints. The following day he developed precordial pain, radiating to the left side of his chest and aggravated by deep breathing. He began to cough, raising moderate amounts of creamy sputum without blood. He was admitted to the hospital, where the temperature was found to be 101.4°F. For the next 4 days it never dropped below 100. The pulse rose to a level of 90 to 120. On admission to the hospital he was given 6 gm. of sulfadiazine, and thereafter received 1 gm. every 4 hours until June 10. The blood level of the drug rose as high as 21 mg. per 100 cc., but the clinical symptoms were unaffected.

On June 1, the patient developed severe joint pains, with redness and swelling of the involved joints. The right knee was particularly severely involved, and was tapped twice, with removal of 30 cc. of turbid fluid, negative to culture.



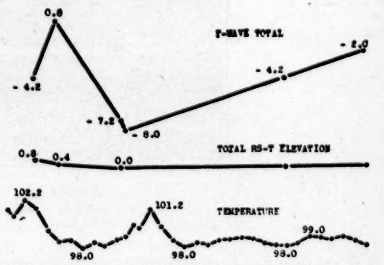


FIGURE 8. *Graph of Findings in Case 7.*

He was started on salicylate therapy on June 10, and the clinical response to 1 gm. of aspirin four times daily was dramatic.

On June 2, a pericardial friction rub was heard for the first time. The precordial aching that had been the first symptom was aggravated and persisted with the rub until June 13. Convalescence was uneventful except for the persistence of electrocardiographic alterations.

CASE 8 (Fig. 9). This 23-year-old soldier was well until January, 1944, at which time he began to lose weight and develop pain in the left chest. A diagnosis of fibrinous pleuritis was made, and he continued to have distress in the chest. On April 25, he was admitted to a hospital, where he was found to have left pleurisy with effusion. A diagnostic thoracentesis was done, with removal of 25 cc. of slightly turbid fluid. Some of this was injected into a guinea pig, but the report of this examination is not available. When the patient arrived at this hospital on June 30, x-ray examination showed a diffuse clouding of the lower two thirds of the left lung field. He was afebrile and complained only of some distress in the left chest on deep breathing.

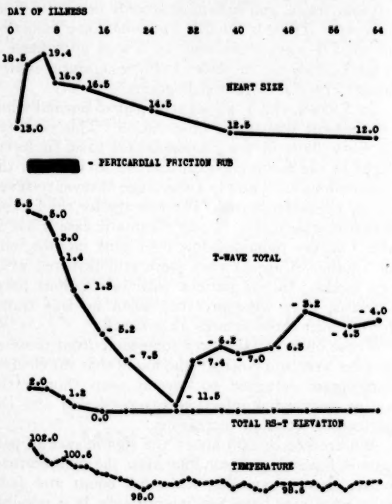


FIGURE 9. *Graph of Findings in Case 8.*

Progress was uneventful until August 1, when the patient developed pain in the left shoulder and the left side of the neck, accompanied by a feeling of substernal pressure. The next day the temperature was 99.8°F., and physical examination revealed a pericardial friction rub in the 2nd and 3rd interspaces to the left of the midline. The following day the temperature reached 102°F. Electrocardiograms showed some elevation of RS–T_2 but nothing else. Chest x-ray examination revealed a marked increase in the transverse diameter of the heart. The pericardial friction rub persisted for 9 days. The temperature went down slowly by lysis, becoming normal on the 20th day and remaining normal thereafter. The heart was largest on the 5th day, thereafter gradually returning to normal, reaching its original size on the 38th day. Progress electrocardiograms showed progressively increasing negativity of the T waves, reaching a maximum on the 25th day. The white-cell counts throughout the acute illness varied between 6700 and 8100, with 65 per cent polymorphonuclear cells. The sedimentation rate was 42 mm. per hour on the 2nd day, 27 mm. on the 7th, 38 mm. on the 12th, 34 mm. on the 15th, 26 mm. on the 22nd, 11 mm. on the 31st, 11 mm. on the 38th, and 12 mm. on the 50th. Improvement was uneventful.

DISCUSSION OF CHARTS

It is to be noted that Cases 1, 2 and 3, although representing three different etiologic agents, present a similar picture (Figs. 1, 3 and 4) when recorded by this graphic method. In all of them, the heart increased rapidly in size, reaching its maximum by the tenth day. At the time of maximum change in heart size there was little or no change in the electrocardiogram, although in Cases 1 and 2 some elevation of the RS–T segment had occurred. In all three the maximum T-wave inversion occurred after the heart had returned to its original size. This is a significant point in diagnosis and will be emphasized later.

T-wave inversion sometimes occurs after the temperature has returned to normal and the patient is clinically well. This is well illustrated in Cases 1 and 2 and may also have been true in Case 3, but there was a long interval during which time no electrocardiograms were obtained.

Of special significance is the fact that the T-wave total in Case 1 was positive throughout. In other words, no single electrocardiogram in this case (Fig. 2) can be considered typical of pericarditis. It was only by repeated examinations that the characteristic picture could be demonstrated on a graphic chart. This point is also worthy of repeated emphasis. The diagnosis of pericarditis by electrocardiograms is frequently impossible without repeated examinations.

In Case 4 (Fig. 5), the patient, who presumably had a tuberculous polyserositis, continued to run an irregular fever after two months of illness. The electrocardiogram and chest x-ray picture remained unchanged during the time that he was at this hospital. The graph is important in again demonstrating that the maximum T-wave inversion occurs after the heart has returned to a normal or nearly normal size. Also to be emphasized is the fact that the T waves remained inverted as long as this patient was under observation, during which time the pericarditis continued to be active.

A graph was not made in Case 5 because the x-ray films were not available, but this case is of interest in that the T waves remained low for nine months, during which time there was clinical evidence of activity of the rheumatic process.

The patient in Case 6 had a severe rheumatic pericarditis, and it may be seen that the heart had reached its maximum size and was returning toward normal before the T waves reached their lowest point (Fig. 7). The picture is similar to that in Figures 1, 3 and 4, except that the time intervals are much longer.

In Figure 8, it may be seen that the patient (Case 7) was the only one who showed maximum T-wave inversion before the heart had reached its greatest size. Also of interest in this case is the fact that an early T-wave inversion was followed by nearly isoelectric waves and then by more marked inversion. Although occasionally such rapidity of electrocardiographic alteration is seen in acute myocarditis secondary to rheumatic fever or myocardial infarction, it was not seen in the other cases

we have studied or in those reported in the literature, except in a single case reported by Fuller and Quinlan.[11] It is possible that the primary inversion was caused by rapidly accumulating fluid in a pericardial sac that could not stretch. This suggestion is given some support by the fact that the heart never became particularly large, despite the severe degree of T-wave inversion. On the other hand, no evidence of the presence of cardiac tamponade appeared at that time, so that no proof of markedly elevated intrapericardial pressure can be found. The patient was seen at this hospital on about the sixtieth day of his illness. At that time, as may be seen, he was afebrile and the heart had returned to normal size, but he still had T-wave inversion. The sedimentation rate and white-cell count were normal. The T waves became upright within four weeks.

The patient in Case 8 was followed in this hospital throughout his entire course. It may be seen that the x-ray and electrocardiographic changes followed the typical pattern for two months (Fig. 9). The sedimentation rate was normal by the thirty-first day and the heart was normal by the thirty-eighth day. Electrocardiograms showed a rapidly progressive increase in the T-wave inversion until the twenty-ninth day. This inversion was the most marked in this series of cases, totaling 11.5 mm. From the twenty-ninth to the fifty-first day it decreased. From that point it remained unchanged, and at the time this paper was written, on the 73rd day of the disease, the total inversion was the same. The temperature, white-cell count and sedimentation rate were normal and the patient was asymptomatic.

Discussion of Observed Changes

The first change generally referred to in the textbooks is elevation of the RS–T segment. This was noted in 5 of the 7 cases presented but was never extreme, the highest being 2.0 mm. (Case 8). It was a transient change, persisting from sixteen to thirty days. From an etiologic point of view, it was noted in all three of the cases of rheumatic pericarditis and in the single case of meningococcal involvement. It was also present, although minimal, in one of the 2 tuberculous cases and was absent in the patient with pneumococcal disease. It should be carefully searched for in every suspected case of pericardial inflammation, since these graphs clearly show that it is the first demonstrable change. It may, however, be found in normal persons, and serial electrocardiograms are often necessary before an accurate diagnosis can be established.

In this series, the maximum T-wave inversion came between the sixteenth and the forty-third day of disease, with an average of twenty-seven days. Considered according to etiology the figures are sixteen days for the pneumococcal case, twenty-five for the meningococcal, twenty-nine for the tuberculous and thirty-one days for the rheumatic. This time interval should be emphasized, inasmuch as a patient with acute pericarditis may die long before diagnostic T-wave inversion appears.

Sometimes the T-wave inversion does not involve all four leads, and occasionally only one or two are inverted. There is usually, however, some reduction in total T-wave deflection, as is well illustrated in Case 1. This can be shown only by careful measurements in serial electrocardiograms.

In 5 cases, the T waves returned to normal while the patient was under observation. This occurred in forty days in the pneumococcal case, in forty-eight in the meningococcal case, in fifty-two in the tuberculous case, and in an average of seventy-seven in the rheumatic cases. The average for the 5 cases was fifty-nine days. In one rheumatic case (Case 5) the T waves remained low over nine months, and in another (Case 8) they were still inverted after ten weeks. In the patient with tuberculous polyserositis, they were inverted when he was transferred, over three months after onset.

These observations vary somewhat from those of Vander Veer and Norris,[8] who found that the electrocardiogram returned to normal even though the active pericardial infection was persisting and the pericardial effusion increasing.

We are not certain about the significance of persistent T-wave inversion long after the temperature, pulse, chest x-ray film, white-cell count and sedimentation rate have become normal. It is possible that these changes are similar to those seen in cases of myocardial infarction, in which T-wave deviations sometimes persist for many months after the acute incident. In our opinion, however, persistent inversion must be regarded with caution, and it has therefore been our practice to restrict the activities of the patient until the T waves return to normal.

There was no consistent variation in QRS amplitude, although a lowered total deflection has been mentioned as one of the diagnostic signs in acute pericarditis.

In this series, the heart reached its maximum size rapidly. Wolff[12] has asserted that the increase in cardiac silhouette that occurs in acute pericarditis may be due to dilatation rather than to pericardial fluid. In this series, Cases 1 and 4 received pericardial taps to demonstrate the presence of fluid. In all the others there was a roentgenologic diagnosis of pericarditis with effusion.

In this series the pericardial friction rub appeared from the second to the thirteenth day of disease. It was present for four to sixteen days, with an average of nine days. In only 1 case was no rub heard at any time.

Summary and Conclusions

In 8 cases of acute pericarditis observed during a period of three months at Battey General Hospital, a graph was devised to correlate heart size,

total T-wave deflection, total elevation of the RS–T segment, pericardial friction rub and temperature. Elevation of the RS–T segment occurred early, was usually slight and disappeared rapidly. The T-wave total began to decrease soon after onset of the disease, but did not reach its lowest point for about four weeks. Judging from the cases observed, there is no significant electrocardiographic difference in the pericarditis caused by rheumatic fever, tuberculosis or pneumococcal or meningococcal infection.

This graphic method of correlating clinical observations in acute pericarditis emphasizes several points. The diagnosis can seldom be made from a single electrocardiogram. In some of these cases the correct diagnosis was delayed for days or weeks because the typical picture did not appear. The T waves may never become isoelectric or inverted, yet a careful analysis of their total deviation may demonstrate significant alterations. Total inversion is a late finding, usually occurring after the heart has returned to normal size and the fever has subsided. The T waves, however, begin to lose amplitude early in the course of the disease, and it is this progressive change that is most important in early diagnosis. It is not necessary to wait until total inversion has occurred to diagnose pericarditis. By careful daily measurement of the T waves, progressive decrease in amplitude can be detected.

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FALSE-POSITIVE HINTON REACTIONS FOLLOWING CHICKEN POX*

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THE evaluation of the specificity of the various tests for the serologic diagnosis of syphilis has gone through two phases. At one time both the complement-fixation and flocculation tests were considered to be so highly specific that some states accepted them as legal proof of a previous or existing syphilitic infection. During the last fifteen years there has been a re-evaluation of these tests and an increasing appreciation of the fact that certain nonsyphilitic conditions are capable of producing biologic false-positive reactions. Furthermore, the possibility of technical false-positive reactions has been repeatedly demonstrated by the interstate serologic surveys conducted by the Committee on Evaluation of Serodiagnostic Tests for Syphilis of the United States Public Health Service.[1]

The diseases already described as being able to produce false-positive reactions include yaws, pinta, bejel, leprosy, malaria, infectious mononucleosis, vaccinia (variola), tuberculosis, atypical pneumonia, disseminated lupus erythematosus, rat-bite fever, relapsing fever, herpes genitalis, miscellaneous upper respiratory infections, measles, typhus fever, typhoid fever, subacute bacterial endocarditis, Weil's disease, Vincent's angina, diphtheria, glanders, rheumatic fever, mumps, infectious hepatitis, chancroid, lymphogranuloma inguinale, scarlet fever, leishmaniasis, kala azar, trypanosomiasis, tularemia, Rocky Mountain spotted fever, leukemia, pellagra, psoriasis, coronary thrombosis, diabetes mellitus, eclampsia, lead poisoning and acute alcoholism. Other conditions include ether anesthesia, hyperglobulinemia, sulfonamide therapy, menstruation, pregnancy, malignancy and injections of horse serum. Kolmer[1] has recently published an excellent review of the problem, and Davis[2] has evaluated the literature on false-positive tests. The latter believes that the ability of a number of the above listed conditions to produce false-positive reactions has not been adequately demonstrated.

During the last one and a half years we have had occasion to observe the occurrence of transient false-positive Hinton reactions in patients convalescent from chicken pox. A review of the literature fails to reveal any previous observation of this nature except that of Gunn,[3] who in 1930 reported one questionably positive and three definitely positive Wassermann reactions in convalescent serums from 25 cases of chicken pox. No flocculation tests were performed. Since adequate standardization had not yet become widespread prior to 1930,[2] Gunn's results are open to reasonable question.

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Clinical Material

The cases of chicken pox comprised in this study include 11 occurring in Harvard University students hospitalized at the Stillman Infirmary and 11 in children at the New England Peabody Home for Crippled Children. All bloods were carefully drawn and were delivered in person to the Massachusetts Wassermann Laboratory, and the tests were carried out by the same skilled technician, using undiluted serum. Wassermann, Hinton and Kahn tests were performed on each specimen. All but 1 of the patients who developed a positive Hinton reaction during convalescence were known to have had a negative reaction prior to the onset of their illness. Those who developed positive reactions were followed at varying intervals until these became negative. Since the tests were performed in a well recognized serologic laboratory, the possibility of technical error was reduced to a minimum.

Results

In Figure 1 are listed the results obtained on serums from 22 unselected convalescent cases of chicken pox. Five of these patients (22 per cent) developed positive Hinton reactions, and 1 showed a positive Kahn reaction as well. In no case was the Wassermann reaction positive. All but 1 of the patients who developed positive Hinton reactions were healthy adult males. The exception was a girl with tuberculosis of the spine. Since false-positive Hinton reactions have been reported in tuberculosis, the positive serologic reactions obtained in this case may not have been due to chicken pox. It is interesting to note, however, that the Hinton, Kahn and Wassermann reactions were negative in the 5 other cases of bone and joint tuberculosis included in this series.

The earliest positive reaction developed seven days after the onset of the eruption, and in 1 case persisted for fifty-one days. Within eighty-six days all the positive reactions had reverted to negative.

Discussion

From this small series it is evident that positive Hinton reactions may be obtained following chicken pox; in 1 case there was a positive Kahn reaction. This series is obviously too small to reflect the true incidence of biologic false-positive reactions in this disease, but our results of 5 false-positive reactions in 22 cases tested (22 per cent) suggests that this reaction is not infrequent and is possibly as frequent as the false-positive reactions obtained in malaria (16 per cent) and after vaccination (12 per cent[1]).

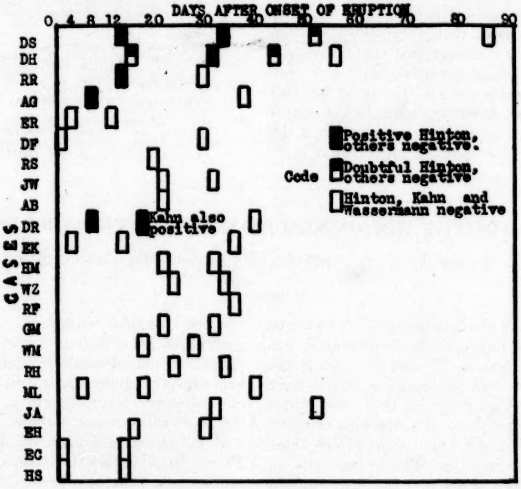

Figure 1.

These results again emphasize the need for a critical approach to the results of serologic tests and careful evaluation of each case before the patient is subjected to the psychologic trauma of a diagnosis of syphilis and the physical trauma of antisyphilitic treatment. The present Army[4] approach to this problem is as follows:

> It is recommended that such individuals who have no conclusive history or clinical manifestations of syphilis

be followed serologically and without treatment for a period of three months, serologic tests being performed each two to four weeks. At the end of this period those in whom the serologic reaction has reverted to negative are discharged from observation as nonsyphilitic; those showing persistently positive tests are regarded as syphilitic, and those still showing conflicting serologic reactions are subjected to further study.

Moore et al.[5] have outlined a suggested clinical approach to the study of this type of case. Mahoney[6] stresses the fact that a certain amount of disagreement in the findings of any two tests is to be anticipated, and observes that these discrepancies may be looked on as a shortcoming of the science of serology rather than as a limitation of an individual technic. That this discrepancy between tests cannot be relied on for the detection of false-positive reactions is brought out by Crawford and Ray's[7] observation that 26 per cent of over 1000 cases considered to be syphilis showed positive Hinton and negative Wassermann reactions.

Summary

Twenty-two unselected cases of chicken pox are presented, 5 of which exhibited transient false-positive Hinton reactions for syphilis. In addition, 1 patient developed a transient positive Kahn reaction. No false-positive Wassermann reactions were obtained. The need for a critical approach to serodiagnosis is again emphasized.

We are indebted to Miss G. O. Stuart, of the Wassermann Laboratory, for performing the serologic tests and to Dr. G. N. Hoeffel for permission to use the clinical material at the New England Peabody Home for Crippled Children.

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MEDICAL PROGRESS

THE PARENTERAL USE OF VITAMIN PREPARATIONS (Concluded)*

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Niacin

Niacin (nicotinic acid) is another water-soluble member of the vitamin B complex. In whole blood, its concentration varies between 0.3 and 0.9 mg. per 100 cc., 90 per cent of this amount being present in the corpuscles as a constituent of co-enzymes I and II.[71–73] The plasma content of niacin, apparently in the free form, ranges between 0.05 and 0.24 mg. per 100 cc.[72, 73]

When niacin is injected, its amide (nicotinamide, niacin amide) should be used to avoid the distressing flushing reactions that attend the parenteral administration of niacin itself. The injection of large doses of nicotinamide intravenously or intramuscularly is followed by a definite rise in the total niacin content of the blood, but the rise and its duration (one to four hours) are small in proportion to the dose given.[72] Of the administered nicotinamide, some is probably methylated in the liver[74]; but the metabolic fate of the major portion is unknown since the amount of niacin or its known derivatives that can be recovered in the urine after the administration of a test dose usually does not exceed 10 per cent of that dose.[73, 75]

Niacin itself is present in quite small quantities in human urine, and its urinary excretion does not increase appreciably after nicotinamide is given, whether intravenously (200 mg.[76]) or orally (500 mg.[77] and 50 mg.[78]). A methylated nicotinamide derivative, variously identified as trigonelline,[76] fluorescent pigment F_3,[79] N-methyl nicotinamide[74, 78–80] and nicotinamide methochloride,[81] has, however, been identified in human urine. Since this derivative constitutes over 90 per cent of the known niacin products in the human urine,[78] and since many authorities (but not all[75]) believe that its urinary excretion is an index of niacin stores, saturation tests have principally relied on the measurement of the methylated nicotinamide in the urine.

In normal subjects, 200 mg. of nicotinamide, whether given orally or intravenously, was followed by an 18 to 30 per cent urinary recovery (as trigonelline) in the next twenty-four hours.[76] Doses of 500 mg. were followed in a twelve-hour period by a 90-mg. average excretion in normal adults and a 41-mg.

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average excretion in hospital patients.[82] Again the results were similar, whether the nicotinamide was given orally or intravenously. Only 10 per cent of an intravenous dose of 5 mg. per kilogram was recovered, chiefly as trigonelline, in the urine by Field and his associates.[72] Ellinger and Benesch[83] testing for nicotinamide methochloride, obtained a 12 to 13 per cent recovery in twenty-four-hour urine collections after 100 mg. of nicotinamide had been given orally or subcutaneously to normal subjects. On the other hand, Najjar[79] found that an oral dose of 100 mg. of nicotinamide was followed by a urinary excretion of 2.1 to 4.0 mg. of N-methyl nicotinamide in four hours, but that somewhat larger excretion figures were obtained with parenteral load tests. Similarly, an oral dose of 50 mg. in children with nonhepatic disease was followed by a 3 to 7 per cent excretion in four hours, whereas the excretion ranged between 5 and 12 per cent after 20 mg. had been given intravenously.[74]

Although the urinary excretion of niacin after load tests with nicotinamide may be decreased in pellagrins and other patients with low niacin stores, it does not appear possible to saturate man with nicotinamide, as can be done with vitamin B_1 or riboflavin. The daily ingestion of large doses (50, 100 and 200 mg.) of nicotinamide, for example, increases the urinary output of the vitamin but moderately[76] or not at all.[78, 81] The reason for this is not clear. Either nicotinamide is stored or destroyed in the body no matter how much is given in excess of the body's needs, or all its derivatives appearing in the human urine have not yet been identified.

On the basis of what is known concerning niacin metabolism and excretion, it appears that less than 20 per cent, and often no more than 10 per cent, of a dose of nicotinamide is excreted in the urine. The figures are not affected by the size of the dose and are only slightly influenced by the route of administration. In deficient subjects, the urinary loss may be less, but it does not increase markedly in subjects who should theoretically be saturated.

Requirement. The National Research Council[1] recommends 18 mg. of niacin daily for a moderately active male of 70 kg. This allowance is suspected of being far above the minimum needs,[77] but actually, knowledge of the human requirement for niacin is extremely scanty.[84] Obviously, the relatively unsatisfactory state of saturation tests with niacin or its amide contributes to the uncertainty that beclouds knowledge concerning man's niacin needs.

By analogy to other vitamins, it is assumed that the requirement for niacin is roughly parallel to one's total metabolism. Thus, 6 mg. of niacin is recommended per 1000 calories for the normal person.[1] In illness, 10 mg. of nicotinamide per 1000 calories may be suggested as an adequate dose for parenteral administration, although the influence of fever, starvation and thyrotoxicosis on man's niacin requirement is totally unknown.[35] Man's capacity to store niacin or its derivatives is also an unexplored subject,[75] although studies in dogs (which, incidentally, can be saturated) suggest that a limited storage of the vitamin occurs.[85] By analogy with riboflavin, one may suggest that the daily parenteral dose of 10 mg. per 1000 calories should be supplemented with 40 mg. of nicotinamide if it appears that the patient has had a deficient intake or absorption of this vitamin for more than two weeks, or if he is being subjected to roentgen therapy.[46] The total daily dose would then be 60 to 70 mg. of nicotinamide or about one third of the daily dose recommended by Spies[42] for the treatment of mild pellagra.

Certain diets seem to influence man's requirement for niacin,[84] but the effects of parenteral water, glucose, saline solution, amino acids and other vitamins are unknown. As is true of riboflavin, however, niacin storage in rats appears to be promoted when the animals are adequately supplied with protein.[65, 66]

Biosynthesis of nicotinamide is not only said to occur in the human intestine, but it is also believed to contribute a substantial part of the nicotinamide requirement.[83] The administration of sulfonamides that act principally within the gut's lumen depresses this biosynthesis.[83] Whether the nicotinamide thus formed is available or nutritionally significant during periods of illness or complete starvation is unknown.

Other Members of the Vitamin B Complex

Many other water-soluble members of the vitamin B complex have been identified and studied. Two that have been synthesized and are commercially available for parenteral administration are pyrodoxin (vitamin B_6) and pantothenic acid (often sold as its sodium or calcium salt). It has not been established unequivocally, however, that pyridoxin and pantothenic acid are essential for man, and the part, if any, played in human nutrition by these two factors has not been defined.

In man, the concentration of pantothenic acid has been reported as ranging from 19 to 32 microgm. per 100 cc. of whole blood in one series[86] and from 3 to 9 microgm. in another.[87] Following the intravenous injection of 100 mg. of either calcium or sodium pantothenate, a procedure that causes no reactions, blood levels and urinary excretion of pantothenic acid undergo a transient elevation.[88] In dogs, the following contrast in urinary excretion obtains after oral and intravenous administration of pantothenate:

DOSE	TWO-HOUR EXCRETION
mg./kg.	%
1 (orally)	0
1 (intravenously)	25
4 (orally)	1–5
4 (intravenously)	41–57

The short period of urine collection may have influenced these results, but the peak in the excretion passed before the end of the two-hour period, even in the oral tests.[89]

A pantothenic acid intake of 10 or 11 mg. per day has been estimated to be a safe level for man.[8, 90] In adult dogs, large daily doses of calcium pantothenate (40 mg. orally) seem to bring about enough storage of this substance so that the dogs can subsist for two or three months on a diet deficient in pantothenic acid.[91]

Pyridoxin excretion in the urine contrasts with pantothenic acid in that the excretion of the former appears to be independent of the route of administration. An oral dose of 100 mg. of pyridoxin in man is followed by a 7.5 per cent recovery in the urine four hours later.[92] After an intravenous dose of 50 mg., the urinary recovery in one hour lies between 8 and 9 per cent,[92, 93] a figure that is practically identical with the results of the oral test. In spite of the apparent ability of the body to "take up" injected pyridoxin, one should be cautious in concluding that the huge doses that have been recommended for certain disorders such as irradiation sickness or agranulocytosis are actually economical and rational from the viewpoint of the body's ability to utilize this substance. It should be recalled that the assay for pyridoxin and knowledge concerning its metabolism and that of related compounds leave considerable room for improvement.[8]

On the basis of indirect evidence, man's "requirement" for pyridoxin has been set at 1.5 mg. per day.[90]

Although the role of pyridoxin and pantothenic acid in human nutrition is still uncertain, there is little doubt that vitamin B complex contains factors essential for man's health. Chiefly on the basis of animal experiments, vitamin-like activity has been ascribed to various substances, of which biotin, inositol, choline, para-aminobenzoic acid and folic acid (*Lactobacillus casei* factor) are among the better known.[94] Most of these factors are untried entities so far as human nutrition is concerned; but some of them, or others as yet unknown, must account for the fact that sources of vitamin B complex, such as brewer's yeast, supply man with nutritious principles that are lacking from pure preparations of thiamine, riboflavin, niacin, pyridoxin and pantothenic acid.

In order to supply vitamin B complex parenterally, recourse must be had to parenteral liver extract. Heretofore, crude liver extracts — that is, extracts containing 1 or 2 units of antipernicious anemia factor per cubic centimeter — have been used for this purpose, in the belief that the concentration of the various other factors would be decreased in preparations containing 15 units of anti-pernicious anemia factor per cubic centimeter. The fallacy of this belief is demonstrated in an extremely important paper by Clark,[95] who shows that concentrated liver extract (an average of four preparations containing 15 units of anti-anemic factor per cubic centimeter) contains 1.9 times as much riboflavin, 1.1 times as much niacin, 1.1 times as much pantothenic acid and 2.2 times as much *L. casei* factor as does an equal amount of crude liver extract (2 units per cubic centimeter). The concentration of thiamine in parenteral liver extract is minimal. Furthermore, Clark shows how markedly the nutrition of the animals whose livers are used and the methods of preparation employed by different manufacturers affect the concentrations of the vitamin B components in the final product. In one concentrated extract, for example, the riboflavin content was 205 microgm. per cubic centimeter, whereas in a crude extract it was only 1.2 microgm. Similarly, the concentration in micrograms per cubic centimeter ranged for niacin between 109 and 3161, for pantothenic acid between 5 and 1710, and for *L. casei* factor between 0.2 and 8.72. Clark's figures do not include all the vitamin B fractions, but the sample suggests that the concentrations of other nutritional factors in parenteral liver extracts are subject to an equally great variation. In view of these facts, it would be most advantageous if manufacturers analyzed some of their liver extracts for the known vitamin B fractions and printed the results on the label. It is true that some preparations to which thiamine, riboflavin and niacin are added are labeled, but the figures on most of these preparations indicate the amounts of synthetic vitamins added and tell nothing of the vitamin B content of the liver extract itself.

Obviously, no definite indications for parenteral vitamin B complex therapy can be given. To certain patients, however, whose intake or absorption of the factors comprising the vitamin B complex has been impaired for more than four weeks, intramuscular injections of liver extract can be given with advantage. Such patients include those with chronic ulcerative colitis or sprue and those who, after prolonged pyloric obstruction, are subjected to gastrectomy with complete, if temporary, elimination of food by mouth. So far as one can judge clinically, the functional disorders that often follow gastrectomy[96] are at times greatly ameliorated after parenteral liver extract is given.[97] The dosage, as can be deduced from Clark's figures, is anyone's choice. Three to six cubic centimeters (always intramuscularly, never intravenously) weekly is used by many. Since the available information suggests that the concentrations of the vitamin B components are not greatly different in the crude and concentrated extracts, the determining factor in choosing a liver extract for parenteral injection seems to be its cost. On the other hand, crude extracts may contain essential substances that have not yet been identified.

Vitamin C

The concentration of vitamin C (ascorbic acid, cevitamic acid) in the human plasma ranges be-

tween 0.3 and 1.8 mg. per 100 cc.; levels of 0.8 mg. or over occur in those whose intake of vitamin C is ample.[98–100] Whole blood concentrations average 0.1 to 0.2 mg. per 100 cc. higher,[98] chiefly because of the high vitamin C content of white cells (25 to 38 mg. per 100 cc.[99]). In red cells, the level is 0.4 to 1.5 mg. per 100 cc.[99]

Ascorbic acid is water soluble and is suitable for parenteral injection, preferably as sodium ascorbate. Following intravenous injection, the plasma level rises markedly, but within a few hours most of the excess vitamin is removed from the plasma.[101] Unlike thiamine or riboflavin, vitamin C appears to have a renal threshold that varies from person to person but usually lies between 1.1 and 1.8 mg. per 100 cc. of plasma.[101, 102] Once its plasma level is in excess of the threshold, ascorbic acid is excreted in the urine, the rate of excretion depending on the plasma level, the rate of glomerular filtration and the maximal rate of tubular reabsorption.[103] Thus, if the plasma vitamin C level is 5 mg. per 100 cc., the glomerular filtration rate 120 cc. per minute, and the maximum rate of tubular reabsorption 2.16 mg. per minute,[103] about 4 mg. of the vitamin is excreted in the urine per minute. The rate of urine flow does not affect the amount of vitamin excreted.[103] In man, the maximal rate of tubular reabsorption of vitamins is not impaired by infusing glucose solutions, even when the plasma glucose level is raised above 300 mg. per 100 cc.[103] In dogs, on the other hand, simultaneous intravenous administration of glucose and ascorbic acid is said to decrease the tubular reabsorption of ascorbic acid and thus lead to an increased excretion of the vitamin.[104]

Since the intravenous injection of a saturation-test dose of vitamin C is much likelier to elevate the plasma level than an oral dose of the same size, a definite difference in urinary excretion of vitamin C is expected between the two methods of administration. On the whole, this tends to be the case. In deficient patients, the urinary excretion of ascorbic acid five hours after 400 mg. had been given orally totaled only 2 to 5 mg.; after the intravenous injection of the same dose, it amounted to 30 to 80 mg.[105] In another series, unsaturated subjects excreted less than 20 per cent of a 100 or 200 mg. test dose in 24 hours, whether it was given orally or intravenously.[106] Saturated subjects, however, excreted 60 to 100 per cent, with the loss slightly larger after intravenous injection. Faulkner and Taylor[101] found a more marked difference; their deficient subjects excreted only 20 mg. in twenty-four hours after 1 gm. of vitamin C had been given orally, whereas they excreted 296 mg. after an intravenous test dose. Normal subjects reported in their study excreted 200 mg. after taking 1 gm. by mouth and 403 mg. after receiving this dose by vein. When 200 mg. was given intravenously to apparently normal soldiers, an average of roughly 15 per cent (range, 5 to 103 mg.) was recovered in the urine six hours later.[107] In a deficient subject, 1.5 gm. of vitamin C given orally was followed by an 82-mg. loss in the urine within twenty-four hours, whereas the loss in a comparable subject after the same dose had been given by vein was 582 mg.[98] On the other hand, a deficient subject excreted only 134 mg. after an intravenous administration of 1.5 gm. It is thus apparent that intravenous injection of vitamin C leads to spillage in the urine.[108, 109]

On the other hand, the avidity of the tissues for ascorbic acid plays a major role: vitamin C is apparently removed so rapidly from the plasma of a deficient subject that the plasma level soon drops below the renal threshold, even after intravenous injection of the vitamin. So far as the parenteral ascorbic acid therapy of patients is concerned, the urinary loss after rapid intravenous infusion in moderately depleted subjects averages about 20 per cent, in normal subjects about 40 per cent, and in saturated subjects over 80 per cent.[110] A slow infusion of vitamin C diluted in saline solution presumably entails less of a loss, especially if the amount of ascorbic acid given per minute is extremely small and if the recipient's need for the vitamin is great.

Requirement. The adult man of 70 kilograms is thought to need 75 mg. of ascorbic acid a day, and a lactating woman 150 mg.[1] As holds true for other vitamins, these allowances are thought by some to be safe rather than minimum.[100, 111, 112] When fever is present, the metabolism of vitamin C may be altered.[35, 113] Plasma ascorbic acid, for example, is lowered during the course of an infectious fever but not during an artificial fever induced by mechanical means.[114] Another author believes fever may lead to the destruction of 100 mg. or more of ascorbic acid daily,[115] but the evidence for this is not clear cut.[35] Leukemia, or its treatment, is said to destroy vitamin C in the body,[98] and the requirement for the vitamin may be increased in hyperthyroidism.[38] When saturation tests are used, a patient with an infection may excrete no more ascorbic acid than a scorbutic subject.[101] According to Harris and his co-workers,[116, 117] the requirement for vitamin C is increased in osteomyelitis, Addison's disease and systemic infections. Although ascorbic acid is excreted in sweat, the amount thus lost is minimal.[33] Finally, various drugs and high altitudes may affect the metabolism of vitamin C.[118] In view of the high allowance recommended for a lactating woman, and the scattered suggestions that ascorbic acid consumption is increased in febrile illnesses, a 200-mg. dose of vitamin C may be suggested as a daily maintenance dose for the patient who requires parenteral administration of the vitamin. A 25 per cent loss in the urine would still leave 150 mg. for the patient's needs. It should be noted that this dose is considerably less than the 500 mg. per day recommended by Wolfer and Hoebel,[119] but exceeds the 50 mg. advocated by Spies.[43]

No large stores of vitamin C can be laid down in the human body.[10] On the other hand, a saturated patient suffering from tuberculosis can stay on a vitamin C deficient diet for "several weeks" before his plasma level falls below 0.78 mg. per 100 cc.[101] In the classic experiment of Crandon et al.,[120] the plasma level fell below 0.8 mg. per 100 cc. almost immediately after a normal subject, previously on an average diet, started a diet poor in vitamin C. In forty-one days, the level was zero. Definite symptoms and signs of deficiency did not appear, however, until the subject had abstained from ascorbic acid-containing food for four months. Thus, although it may take some time for severe tissue depletion of vitamin C to occur, it appears advisable to give vitamin C parenterally to any patient who is unable to take the vitamin by mouth or who is presumed to have had a deficient intake for a week or more.

The plasma level of vitamin C as an index of a patient's ascorbic acid stores has had its supporters and its detractors. For clinical purposes, however, it offers a fairly simple and not too inaccurate means of gauging a patient's status with respect to vitamin C.[98, 100, 111] Hence, if facilities are available for quantitating the plasma vitamin C content, much less guesswork must be used in estimating the needs of the depleted patient. If such facilities are not available, one must again be guided by extremes. A patient with frank scurvy has to ingest 700 mg. of vitamin C daily for seven to ten days (total, about 5 to 6 gm.) before he becomes saturated.[121, 122] For normal subjects who have depleted their stores by subsisting on a vitamin C-poor diet, 100 mg. by mouth daily for a month saturates the tissues adequately.[118] When 1 gm. is given daily by intravenous injection, a total of 4 to 6 gm. is needed to resaturate a normal subject with experimental scurvy.[120] In a patient with laboratory evidence of low vitamin C stores (low plasma level and low urinary excretion after a saturation test), a total of 1.5 to 2.8 gm. appears necessary to achieve saturation.[98] Consequently, if a patient requiring vitamin C by parenteral routes is believed to have deficient stores of this vitamin, either because of his dietary history or because of low plasma ascorbic acid levels, 500 mg. daily for a week appears to be sufficient to build up his stores. If there is great urgency, 1 to 2 gm. can apparently be given intravenously with satisfactory results.[98]

Vitamin A

The parenteral injection of the fat-soluble vitamins, of which vitamin A is one, presents special problems unless water-soluble preparations are available. The intravenous administration of finely emulsified fats is possible, but the preparation and preservation of such emulsions are not easy, and none are sold for general use. The intramuscular route is, of course, frequently used, but, as is evident if one follows the fate of radio-opaque oil that has been given intramuscularly, months may pass before most of the material is mobilized from the site of injection.[123] Obviously, any fatty vitamin administered intramuscularly cannot be expected to provide the recipient with a large dose that is immediately available for the body's needs.

When measured with the technic commonly used in clinical studies, the plasma level of vitamin A normally lies between 30 and 80 microgm. (100 to 250 *U. S. P.* units) per 100 cc.[124, 125] The carotene (provitamin A) concentration is usually 40 to 200 microgm. per 100 cc. of plasma.[5, 124] With microtechnics, somewhat lower vitamin A levels are obtained.[126]

When large doses (75,000–100,000 units) of vitamin A are injected intramuscularly in man, the plasma level of the vitamin is not elevated.[127, 128] Even in sprue and celiac disease, disorders characterized by a severely impaired intestinal absorption of fat-soluble vitamins, massive oral doses may produce a small rise in the vitamin A level of the plasma,[129, 130] but the same doses intramuscularly are without such an effect.[129] This fact does not necessarily mean that intramuscular administrations are ineffective. In patients with obstructive jaundice, the livers of those who have been treated with intramuscular vitamin A contain on the average more of this vitamin than do the livers of untreated patients.[128] Judged on the basis of growth effects and hepatic storage, animals use vitamin A equally well, whether given orally or parenterally[131, 132] The literature on this point, however, does not report uniform results, others stating that vitamin A given intramuscularly to rats is only 10 to 15 per cent as effective as the same amount given orally.[133] It seems reasonable to conclude as follows: the oral route is incomparably better than the intramuscular for the administration of vitamin A. Parenterally injected vitamin A is probably available for utilization, but the rate of its liberation from the injection site is so slow and the rate of metabolism or storage is so rapid that the plasma level is not materially changed. The urinary excretion of vitamin A is not significant.

Vitamin A in propylene glycol is well utilized by rats after intramuscular injection,[132] but 70,000 units of the same preparation does not elevate the plasma level in human subjects and produces considerable pain at the injection site.[97] The utilization of carotene after parenteral injection is even less efficient than that of vitamin A.[131]

Unlike the water-soluble vitamins, vitamin A can be stored in large quantities in such depots as the human liver. Twelve million, five hundred thousand units given by mouth over the course of five days can raise the average hepatic concentration of vitamin A from 100 to 366 microgm. per gram of fresh liver tissue.[134] Once well fortified with oral doses of vitamin A, normal subjects can subsist for

six months on a diet deficient in this vitamin without decreasing their plasma level of vitamin A.[135]

The daily requirement of vitamin A for the adult has been set at 5000 units. Whether there is an increased requirement for vitamin A, or rapid depletion of its stores, in disease is difficult to tell. An almost endless list of diseases, it is true, may be associated with a decrease in the plasma level of vitamin A, but this level is too dependent on other factors, such as hepatic function, to serve as a good index of the body's stores. As Popper and his associates[134] have said, a high plasma level often suggests high or normal liver stores, but the reverse does not hold true.

In view of the body's ability to store vitamin A and the rather unsatisfactory results obtained from its intramuscular use, sound indications for injecting vitamin A parenterally occur but rarely. Conceivably, patients with a long-standing exclusion of bile from the gut, or with steatorrhea from other causes, may benefit from such injections, but even in these cases, large oral doses — that is, about 250,000 units daily — probably increase body stores more efficiently. Whenever possible it seems reasonable to build up a patient's vitamin A reserves by means of several large oral doses before any operation is undertaken that might interfere with food ingestion or absorption for a protracted period of time.

Vitamin D

Vitamin D, a fat-soluble vitamin, appears in plasma in concentrations ranging from 66 to 165 *U. S. P.* units per 100 cc.[136] After oral administration of huge doses (50,000 to 500,000 units), the plasma concentration of vitamin D may temporarily approach that of cod-liver oil.[136] Following the administration of such large amounts, considerable storage of the vitamin presumably occurs, since three to six months elapse before the vitamin D content of the plasma returns to normal.[136] Corroborative evidence of the body's capacity to store vitamin D is obtained from the facts that a single large dose of calciferol (vitamin D_2, irradiated ergosterol) protects infants against rickets for eight to twelve weeks[137] and provides puppies with adequate growth for one year.[138] A peculiar feature of this storage is that tissue analysis for vitamin D fails to reveal any capacious storage organ for the vitamin.[138]

Vitamin D is apparently utilized when given by the intramuscular route, for protection against rickets has been achieved in infants by giving 600,000 units of either vitamin D_2 or D_3 (activated 7-dehydro-cholesterol) parenterally.[123, 139, 140] If the oily solution containing the vitamin D_3 is diluted by ether, it is said that the absorption from the intramuscular injection site is more rapid, and that rachitic phenomena regress as promptly as after oral therapy.[123] In other studies, the parenteral injection of vitamin D_2 was much less effective than injected vitamin D_3 in treating infantile rickets.[141] In chickens, the utilization of vitamin D appears to be enhanced if vitamin D in propylene glycol is used for parenteral injections.[142]

One may therefore conclude that vitamin D injected intramuscularly is in large part available for metabolic uses. On the other hand, the requirement of the adult for this vitamin is uncertain,[1] and it appears that storage is adequate to provide for fairly long periods of depletion. Hence it is doubtful that parenteral injections of vitamin D have to be used in maintaining the nutrition of a patient who is unable to take this vitamin orally.

Vitamin E

The serum tocopherol (vitamin E) level, as determined by chemical methods, ranges between 0.60 and 1.60 mg. per 100 cc.,[143, 144] but lower levels, averaging 0.20 mg. per 100 cc., have also been reported.[145] Oral administration of vitamin E elevates the serum tocopherol level,[143] but as in the case of vitamin A, intramuscular injections (100 mg. of alpha-tocopherol) do not.[144] In rabbits, the intramuscular injection of oil-soluble tocopherols is also ineffective in curing the signs of deficiency,[146] but a water-soluble preparation is said to be curative when given parenterally.[147]

Storage of vitamin E occurs in the liver[148, 149] and in the abdominal fat[150] of the rat. In human livers, a somewhat similar storage may take place.[148] Vitamin E is not excreted in the urine.[149]

Vitamin E has been administered to patients for a great variety of illnesses, chiefly those of the neuromuscular system, but the effects of tocopherol deficiency in man are undefined. For this reason, the significance of vitamin E in human nutrition is uncertain, and daily allowances that have been suggested on the basis of interesting but indirect evidence[151] must await further study before they can be accepted.

Vitamin K

Naturally occurring vitamin K is a fat-soluble substance that appears to be utilized by the liver in making prothrombin. At present, the vitamin K content of the blood cannot be measured directly, but the blood's prothrombin concentration provides a good index of the availability of vitamin K to the body, provided the patient does not suffer from hepatic disease and has not been treated with dicumarol.[152]

The situation with respect to vitamin K is rather unusual in that the naturally occurring substances with vitamin K activity have been supplanted by an equally active synthetic product, menadione (2-methyl-1, 4-naphthoquinone). This material is fat-soluble and suitable for intramuscular injection. A related series of water-soluble compounds has,

however, been synthesized: tetra-sodium 2-methyl-1 4-naphthohydroquinone diphosphoric acid ester (Synkayvite), 2-methyl-1, 4-naphthohydroquinone sodium bisulfite (Hykinone) and 4-amino-2-methyl-1-naphthol hydrochloride (Synkamin).

The water-soluble nature of these compounds makes them suitable for intravenous use and preferable to menadione for intramuscular use when, as is often the case, immediate availability of the vitamin is desired.[153] On the other hand, the use of these compounds from the viewpoint of dosage is unsatisfactory, since the manufacturers merely give the total weight of the menadione derivative on the label and do not indicate its vitamin K activity in terms of simple menadione. When an ampule contains 4 mg. of Hykinone, for example, only 2.5 mg. of material with vitamin K activity is actually present.[154] The same holds true for Synkayvite, but here the situation is further complicated by the fact that this substance, although only half as potent as menadione on a weight-for-weight basis, is said to be one and a half times as effective when the substances are compared molecule for molecule.[155–157] Thus, when a certain weight of these water-soluble compounds is injected, only a part — roughly 50 to 70 per cent — of the dose can be considered to have vitamin K activity.

The nature of a substance with vitamin K activity and the route of its administration determine to some extent the rapidity of its action and the duration of its effect. When colloidal vitamin K_1, a naturally occurring compound, is given intravenously to patients with obstructive jaundice, a rapid increase in prothrombin concentration occurs within four hours, and normal prothrombin times are maintained for about two days after a 0.4-mg. dose, and for ten to twenty-five days after a 10-mg. dose.[153, 158] Similarly, 10 mg. of colloidal menadione intravenously effects normal prothrombin levels for ten days.[153] In these instances, a fatty vitamin is rapidly made available to the liver but no obvious loss of the vitamin occurs. When water-soluble preparations are given intravenously, however, the beneficial effect may be less pronounced, and only of short duration.[158] A similar result is reported by Kark and Souter,[159, 160] who found that intravenous injections of a water-soluble derivative of menadione (the bisulfite complex) increased the concentration of prothrombin for only one or two days, whether the amount injected was the equivalent of 1 or 6 mg. of menadione. An intramuscular dose of the same bisulfite complex, equivalent to 2 mg. of menadione, was effective, however, for several days. It has therefore been suggested that water-soluble substances with vitamin K activity, when given intravenously, offer a rapid but temporary supply of vitamin K to the liver, the transient character of the effect being ascribed to urinary excretion or destruction of the vitamin.[153, 159, 160] Except when the circulation is impaired, intramuscular injection of the water-soluble vitamin K preparations reduces the prothrombin time practically as quickly as the intravenous, but presumably less loss occurs since the whole dose is not delivered to the blood stream instantaneously. For long-term therapy, the intramuscular use of menadione itself (in oil) is perfectly satisfactory.

In 1940, Dam[161] stated that 5 to 10 mg. of menadione daily is "entirely sufficient" for an adult person. Clinical studies suggest that this dose amply provides for the needs of patients. Two milligrams of menadione given to jaundiced and hypoprothrombinemic patients has, in the absence of liver disease, restored prothrombin levels to normal for almost a week,[162] and in one case with an absorption defect the same dose apparently sufficed for a whole month.[163] According to studies already quoted, 1 mg. of vitamin K_1 per day is sufficient to prevent hypoprothrombinemia.[153, 158] Ten milligrams of a water-soluble vitamin K analogue given subcutaneously maintained normal prothrombin times for two to three days in patients with evidence of vitamin K deficiency.[164] Andrus and Lord[165] recommend 2 mg. of menadione every three to ten days. In infants, 10 mg. of menadione prevented a fall in the blood's prothrombin concentration for at least twenty-six to twenty-eight days,[166] and 1.25 mg. of a water-soluble preparation was effective in reducing a prolonged prothrombin time to normal and maintaining it in this range.[167] It has also been concluded that a daily dose of 0.5 to 2 microgm. of water-soluble vitamin K analogues is sufficient to prevent hemorrhagic disease in newborn infants.[167, 168] The daily requirement for an adult on this basis would be about 0.1 mg. per day.[169]

In bile-fistula dogs, one to three months may pass before prothrombin levels begin to fall.[170] Nevertheless, storage of vitamin K, when compared with the storage of the other fat-soluble vitamins, is limited. Because large doses (over 20 mg. daily) of the naphthoquinones may produce a mild hemolytic anemia,[171] extensive studies in man on the storage of vitamin K are not easily feasible. Nevertheless, there is evidence that increasing dosage does not lead to increasing storage, but rather to increasing wastage.[168]

One may conclude that for rapid and effective treatment with vitamin K, the intramuscular injection of the water-soluble preparations is advisable, with the admonition that the injected amount has only 50 to 70 per cent of the vitamin K activity of a similar amount of menadione. If the intramuscular route is employed, 4 mg. of the water-soluble substance every two to three days is probably effective. If the vitamin is given intravenously, 2 mg. daily is suggested as a dose.

In the treatment of hypoprothrombinemia, however, one cannot rely on theoretical requirements; one must be guided from time to time by actual determination of the prothrombin level. Since these

levels are known to drop acutely after operations,[165, 172] a dose of vitamin K equivalent to 4 mg. of menadione may be given daily in the immediate preoperative period. Large doses of vitamin K may also be tried in combating the hypoprothrombinemia of hepatic disease[171] or that following the exhibition of dicumarol.[184]

Biosynthesis of vitamin K occurs actively in the human intestine and may provide a considerable proportion of man's requirements for this vitamin. When sulfonamides, such as sulfaguanidine or succinylsulfathiazole, are used, the biosynthesis of vitamin K drops off sharply.[51, 173] This fact is of practical importance in the treatment of such disorders as ulcerative colitis in which a poor diet, diarrhea and the exhibition of intestinal disinfectants may combine to bring about a vitamin K deficiency.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 31401

PRESENTATION OF CASE

A sixty-eight-year-old man was admitted to the hospital because of inability to speak coherently. The history was obtained from relatives.

Five days before admission, after an evening of normal, quiet conversation, he suddenly asked in a thick, almost incoherent voice to be taken to bed. Since that time he had slept almost constantly and had eaten no food other than liquids. His bowels moved three days before admission. He urinated daily. Two days before the onset of this episode he had experienced nausea and some regurgitation and had vomited several times.

The patient was incoherent, incontinent and uncooperative. He seemed to be suffering from abdominal pain. Examination of the heart and lungs was negative. The abdominal muscles were tense. The liver and spleen were not palpable. A 5-cm. nontender, nonpulsating mass was present in the epigastrium just to the right of the midline. The patient was not aphasic. The left arm and leg were weak, without spasticity. The optic disks were well outlined. There was questionable weakness of the left facial muscles. The tendon reflexes were active. The patellar reflexes were more marked on the left than on the right. Plantar flexion occurred on the right, but the response on the left was equivocal.

The temperature was 99.2°F., the pulse 80, the respirations 25, and the blood pressure 170 systolic, 90 diastolic.

Examination of the blood revealed a red-cell count of 3,400,000, with 12 gm. of hemoglobin, and a white-cell count of 14,400, with 68 per cent neutrophils. The urine was normal. The blood Wassermann reaction was positive. A lumbar puncture five days after admission revealed clear fluid under an initial pressure equivalent to 105 mm. of water; after withdrawal of 6 cc. the pressure dropped to 78 mm. The respiratory fluctuations of pressure were normal. The fluid contained no white cells and 50 red cells per cubic millimeter. The total protein was 29 mg. per 100 cc., and the gold-sol curve was normal. The spinal-fluid Wassermann reaction was negative.

*On leave of absence.

A plain x-ray film of the abdomen showed no definite soft-tissue masses. There was extensive arteriosclerosis of the pelvic arteries.

On the twelfth hospital day the blood pressure fell to 125 systolic, 70 diastolic, and auricular fibrillation appeared. An electrocardiogram showed a PR interval of 0.17 second. The QRS complexes in Leads 1, 2 and 3 were upright; T_1 was flat; T_2 upright, and T_3 inverted. The T waves in Leads CF_3 and CF_4 were upright; the S wave in Lead CF_4 was normal. The serum nonprotein nitrogen was 188 mg. per 100 cc., the white-cell count 6400, and the carbon dioxide 10 milliequiv. per liter.

The temperature suddenly rose from a subnormal level to 101°F., and the respirations became rapid. Rales appeared in the right upper lobe, and x-ray films showed consolidation in that area. He expired a few hours later.

DIFFERENTIAL DIAGNOSIS

DR. JACOB LERMAN: There are two points that I should like to question. Was the tumor mass in the abdomen felt by more than one observer? There is the note that it was felt on physical examination, but x-ray examination did not show a soft-tissue mass. Also, there was one negative urine examination. A little later the man went into uremia. Was there more than one urine examination, and if so, what did it show?

DR. RONALD C. SNIFFEN: There were two urine examinations; both were the same, with the exception that 5 to 8 white cells per high-power field were seen in the sediment on the second occasion. The specific gravity was 1.012.

DR. LERMAN: We know that this man had certain pathologic conditions, which are described for us in the record. He had an acute onset of symptoms initiating the development of a cerebrovascular accident, due either to thrombosis or to hemorrhage. The absence of coma and the presence of premonitory symptoms two days previously make one think it was thrombosis rather than hemorrhage. The resulting left hemiplegia confirms the presence of the cerebrovascular accident. We know that he had syphilis, and he probably had latent neurosyphilis. He may also have had cerebrovascular syphilis. Then we also know that he developed an acute infection, — a terminal infection, — which probably precipitated the auricular fibrillation, drop in blood pressure and uremia.

The two points that are hard for me to explain are the abdominal pain, — although this was only surmise on the part of the examiner, inasmuch as the patient actually complained of nothing, — and the mass in the abdomen.

DR. SNIFFEN: At least four people examined the patient. One was sure about the mass, two were vague, and the fourth did not feel it.

DR. LERMAN: I prefer to take the opinion of the

last examiner, since the mass does not seem to fit any obvious diagnosis.

It would be nice to explain all the symptoms on the basis of one disease, and the one disease that might explain them is syphilis. I have already mentioned the possibility of cerebrovascular syphilis and latent neurosyphilis. The vascular accident could then be due either to syphilitic endarteritis or to rupture of a small aneurysm on a syphilitic basis. Syphilitic endarteritis is much likelier. Can we explain the kidney damage and the resulting uremia on the basis of syphilis? This was obviously not a case of syphilitic nephrosis. It could have been a late type of vascular nephritis, such as one finds in syphilis and which is difficult to differentiate from ordinary vascular nephritis. It may terminate in uremia, like any other nephritis. One might consider the mass in the abdomen as due to an abdominal aneurysm — a thrombosed abdominal aneurysm on a syphilitic basis. Unfortunately we have no data to confirm it, and I am not inclined to accept it.

The mass might have been due to a malignant tumor, such as a tumor of the stomach, gall bladder or pancreas. One might then consider metastasis to the brain and other organs, such as the kidneys. Obviously metastases alone would not cause acute hemiplegia of the sort described. On the other hand, hemorrhage into the appropriate metastasis might give a picture similar to that of this patient. This is only surmise: we do not have enough evidence for it.

Another surmise, also farfetched, is a dissecting aneurysm. The dissection could have worked its way up to occlude the right carotid artery and its way down to the abdominal aorta, where a mass resulting from weakening of the wall of the aorta might have been felt. We have no confirmatory evidence, however, such as occlusion of the great vessels of the leg or the presence of excruciating pain at the onset.

Let us disregard syphilis for the time being and consider a disease that might cause this type of cerebrovascular accident, namely, generalized arteriosclerosis with hypertension. This would certainly explain the hemiplegia. The uremia might have resulted from the effects of a generalized infection on previously damaged kidneys, the previous damage having been on a vascular basis.

I wonder if the x-ray films will help so far as diagnosis is concerned.

Dr. Milford D. Schulz: The only thing that is at variance with what is described in the protocol is that the pulmonary lesion is in the right middle lobe rather than in the right upper lobe. Whether it is due to consolidation or to bronchial obstruction I do not know. There is a lot of calcification in the wall of the aorta, and it goes all the way down to the diaphragm. But the aorta itself can be fairly well traced.

Dr. Lerman: Do you see the mass?

Dr. Schulz: I see no abdominal mass. It could easily be missed, however, because the film is underexposed and a mass would be difficult to differentiate from the liver and kidney.

Dr. Lerman: The pain might have been due to syphilis if we assume that this man had a tabetic crisis; but since there is no evidence of active tabes, we cannot ascribe the pain to it. I am not able to explain the pain, other than on the possibility of its association with kidney damage. Abdominal pain is sometimes seen in impending uremia.

My diagnoses are as follows: arteriosclerotic and hypertensive heart disease; syphilis, including latent neurosyphilis and cerebrovascular syphilis; cerebrovascular thrombosis, probably due to syphilis but possibly to simple arteriosclerosis; terminal pneumonia; vascular nephritis on an arteriosclerotic basis; uremia; and possibly abdominal aneurysm.

Dr. Jost Michelsen: Where was the vascular process in the brain located?

Dr. Lerman: I do not know the exact location.

Dr. Michelsen: Do you think that the cerebral symptoms can be explained by one lesion or do you assume that the patient had several lesions?

Dr. Lerman: He had a left hemiplegia, with left facial weakness.

Dr. Michelsen: How do you explain the difficulty with speech?

Dr. Lerman: The patient had a hemiplegia and difficulty in speech without aphasia, which imply motor difficulty.

Dr. Michelsen: What was the motor difficulty? The patient had a mild facial weakness. We are not told what the defect was. How do you then explain the speech difficulty?

Dr. Lerman: I do not believe that I can, other than on basis of motor weakness.

Dr. Michelsen: What I am driving at is that it is likely that he had more than one lesion. Could he have had multiple emboli? Could he have had auricular fibrillation before he was admitted to the hospital?

Dr. Lerman: Without any previous evidence of auricular fibrillation or anything suggestive of it on admission, one can only make a guess. It is not infrequent for a man of this age to develop auricular fibrillation as a terminal event, with a resulting fall in blood pressure. Such a picture is often seen in patients with ordinary arteriosclerotic heart disease. I see your point, namely, that he might have had several emboli going to different parts of the brain, or several thromboses. I assume, however, that the speech difficulty was purely a temporary motor affair, due to muscle weakness and inco-ordination rather than to aphasia. I have seen it before in patients with a left hemiplegia.

Dr. Michelsen: But one usually finds some evidence for it on examination. The evidence here for such a situation is scanty.

I should also like to ask about the occurrence of cerebral aneurysm on a syphilitic basis. Dr. Sniffen, how many cases of cerebral aneurysm have we seen in which syphilitic etiology was definitely established?

DR. SNIFFEN: It is extremely rare.

DR. LERMAN: I agree; I just put it down as a possibility. Vascular thrombosis on the basis of syphilis is much more frequent.

CLINICAL DIAGNOSIS

Cerebral thrombosis.

DR. LERMAN'S DIAGNOSES

Arteriosclerotic and hypertensive heart disease.
Syphilis, including latent neurosyphilis and cerebrovascular syphilis.
Cerebrovascular thrombosis (right), due either to syphilis or to arteriosclerosis.
Terminal pneumonia.
Vascular nephritis, arteriosclerotic.
Uremia.
Abdominal aneurysm?

ANATOMICAL DIAGNOSES

Cerebral infarct, right: internal capsule and corpus striatum.
Carcinoma of stomach, with extension to omentum and metastases to liver and mediastinal and retroperitoneal lymph nodes.
Hydroureter, hydronephrosis and mild chronic pyelonephritis, bilateral.
Bronchopneumonia.

PATHOLOGICAL DISCUSSION

DR. SNIFFEN: At the time of his death the patient was extremely emaciated.

The brain contained a 1.5-cm. infarct situated in the anterior limb of the right internal capsule and adjacent corpus striatum. Microscopically, the infarct seemed to be of approximately three weeks' duration.

The stomach contained a carcinoma involving the greater curvature and the neighboring anterior and posterior walls. The tumor extended from the pylorus to a point about 13 cm. proximal. The gastric wall was 3 cm. in thickness, but the mucosa was intact and there was no mass in the lumen, merely a diffuse infiltration that had not led to obstruction. The lymph nodes along the greater curvature were invaded, and the omentum and transverse colon were caught up in a firm mass of infiltrated fat, which was probably the mass felt on physical examination. Metastases were present in the liver and retroperitoneal and mediastinal lymph nodes. Tumor masses were found in the pelvis, and these surrounded and compressed the ureters, leading to hydroureter, hydronephrosis and a mild pyelonephritis.

Microscopically the tumor showed a peculiar combination of adenocarcinoma and scirrhous carcinoma with signet-ring cells; it included islands of squamous epithelium. Consequently, I imagine that it can be called an adenoacanthoma.

In addition the patient had a severe bronchopneumonia.

DR. MICHELSEN: What caused the infarct?

DR. SNIFFEN: We found no syphilitic lesion in any part of the body. We saw no tumor cells within the vessels. One large vessel was thrombosed. It was our assumption, therefore, that the infarct was caused by arterial thrombosis.

CASE 31402

PRESENTATION OF CASE

A thirty-eight-year-old married woman was admitted to the hospital because of abdominal pain and abnormal vaginal bleeding.

Eleven days before admission the patient noticed a profuse dark bloody vaginal discharge, which was associated with a sharp stabbing, intermittent pain in the midline just above the pubis that was accompanied by tenderness and a bearing down sensation. These cramps were affected by change in position. She had noticed the usual engorgement and tenderness of the breasts that she associated with menstruation. The following day the discharge had a more normal color. Within five days the pain had become less severe, but it recurred after a pelvic examination.

Forty days before the onset of this discharge she had had her last normal menstrual period. She had always had a regular twenty-eight-day menstrual cycle. She normally had a profuse discharge for three days, which then became scanty for two more days. About two years previously, at the expected menstrual time, she had had bearing down cramps and had passed a single large clot followed by a fairly prolonged discharge, which stopped after ergot had been given. Her physician told her that she had had a spontaneous abortion. Except for this questionable episode, she had never been pregnant, and several years previously lipiodol insufflation was said to have shown that both tubes were blocked. She had had an appendectomy years before.

Physical examination revealed a well nourished and well developed young woman. The heart and lungs were normal. There was a firm tender mass about 5 cm. in diameter in the midline immediately above the pubis. To the right of this was an area of maximal tenderness and slight spasm of the abdominal muscles. A rectal examination was negative. A pelvic examination revealed a firm cervix. The fundus of the uterus appeared to be three or four times its normal size. The uterus was freely movable and irregular, with an attached tender mass

on the left; on the right there was a small egg-sized tender mass. The posterior cul-de-sac was free, but there was some induration in the right vault.

The temperature, pulse, respirations and blood pressure were normal.

Examination of the blood showed a white-cell count of 7400 and a hemoglobin of 12 gm. The urine was normal.

On the fifth hospital day an operation was performed.

Differential Diagnosis

Dr. Frederick A. Simmons: In spite of the fact that the fallopian tubes are said to have been blocked, it is necessary to mention that any thirty-eight-year-old woman with abdominal pain and abnormal vaginal bleeding must be considered as a candidate for an ectopic pregnancy, especially when a mass is felt. Certainly the attack eleven days before admission, which consisted of a dark bloody discharge with severe, cramplike, suprapubic pain, a bearing-down sensation and tenderness, raises that possibility. The facts that she had previously had a twenty-eight-day menstrual cycle and that she was twelve days overdue make ectopic gestation a likely diagnosis. The record does not say how many years she had been married, but it does report that several years previously a lipiodol examination had shown that tubes were blocked.

I have seen several cases in which lipiodol suggested that the tubes were blocked but in which an immediate pregnancy occurred following this test. It is important to emphasize that the interpretation of lipiodol studies for patency of the fallopian tubes is extremely unreliable and that, although it is a necessary procedure in sterility investigation, one should not place too much reliance on the comment that the tubes are blocked, unless, of course, the oil fails to pass the uterine ends of the tubes. It would be helpful to be able to see these films.

The uterus is described as being three or four times its normal size, being movable and irregular, with an attached tender mass on the left. The literature reveals cases in which a uterine pregnancy occurred simultaneously with an ectopic pregnancy, but when pelvic masses are found on both the left and right sides, in addition to an enlarged uterus, the possibility of multiple fibroids presents itself. Since the temperature, pulse, respirations, blood pressure, white-cell count and urine were normal, we are probably not dealing with an inflammatory process, such as pelvic inflammation, a twisted ovarian cyst, tuberculosis of the uterus or adnexa or diverticulitis of the colon. I mention the latter because last winter we had a patient on the Gynecological Service who had vaginal bleeding and a tender mass and was thought to have had cancer of the cervix. Multiple biopsies were negative, and subsequent exploration revealed a ruptured diverticulitis, with a pelvis as "frozen" as that usually seen in chronic pelvic inflammatory disease.

With the abnormal vaginal bleeding, cancer must also be mentioned, and in a woman of thirty-eight, carcinoma of the cervix or ovary is likelier than that of the fundus. Although cancer cannot be ruled out, the sudden onset of the symptoms is somewhat against the diagnosis.

A few months ago, while discussing a similar case in one of these conferences, I purposely avoided an obvious fact, namely, a past history of tuberculosis, which is what the pelvic disease turned out to be. Perhaps this patient's irregular bleeding, sterility, abdominal pain and masses were on the basis of an acid-fast infection, but I doubt it.

Presumably the possibility of pregnancy occurred to the house staff. You will note that operation was not performed until the fifth hospital day, and I suspect that an Aschheim–Zondek test was performed. At any rate the patient did come to an exploratory laparotomy. I am going to assume that the statement that the fallopian tubes were blocked is correct and to say that I do not believe that this woman was pregnant.

I believe that the likeliest diagnosis in this case is multiple fibroids of the uterus, with ovarian cysts, which are usually found with multiple fibroids. It would not be surprising, however, to find that she had an exacerbation of long-standing bilateral pelvic inflammation, since abnormal bleeding does occur in such cases.

Clinical Diagnoses

Fibroids of uterus.
Tubal pregnancy?

Dr. Simmons's Diagnoses

Multiple fibroids of uterus.
Simple cysts of ovaries.

Anatomical Diagnoses

Tubal pregnancy.
Multiple leiomyomas of uterus.
Chronic salpingitis.

Pathological Discussion

Dr. Benjamin Castleman: Apparently an Aschheim–Zondek test was not performed; at least there is no note in the record to that effect.

At operation a hemorrhagic mass was found in the outer end of the right salpinx, which proved to be an ectopic pregnancy. The fimbriated ends of both tubes were destroyed and scarred — a finding that is consistent with an old inactive inflammatory process. The uterus contained multiple fibroids, the largest, which measured 9 by 5 by 5 cm., being subserosal and placed anteriorly on the right. The intramural fibroids varied from 1 to 3 cm. in diameter. A subtotal hysterectomy and right salpingo-oöphorectomy were performed.

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"TURN BACK, O MAN, . . . "

There is a doubt today in the minds of many of us how far science can be trusted: a feeling that the cunning with which man has been endowed has betrayed his philosophy and his emotional balance. Our ingenuity, we suspect, has developed far beyond our ethical capacity to guide it, as if a child had released the brakes and engaged the clutch of a machine too powerful and too swift for his control.

It is not a new idea that man, cursed with an obsession for destruction, has been given an inventive genius that far transcends the conservative limitations of his intellect and his conscience. Phaeton drove the chariot of the sun high, wide and handsome but completely off its course until a well directed thunderbolt unseated him; Icarus with his wings of wax, which were in direct competition with his feet of clay, was probably the mythological inspiration of Darius Green; the car of Juggernaut was built by man and proved to be a man-destroyer; and the creation that Frankenstein introduced, made apparently in his own image, turned out to be only his undoing.

There seems to be little in discovery that is good that is not at least counterbalanced by its possibilities for evil. Almost no labor-saving device has been developed that has not had its unfortunate consequences, if only in a weakening of man's moral and physical fiber, just as the old ships of wood with men of iron were supposed to have been replaced by ships of iron manned by men of wood (a comparison, by the way, that recent years have shown to be not entirely true). The benefits that have accrued to man from the invention of the airplane are but a drop in the bucket compared to its overwhelming development as an instrument of destruction.

And now we have the climax-capping discovery of a practical method of unleashing the energy of the atom in a cataclysm of destruction that makes firecrackers of Jove's thunderbolts. It is another discovery of a new instrumentality that will end all wars, as it was instrumental in ending the second world conflict, until the next war begins, when it may easily end man's dominance in a world that he has used so ill. We might entertain the thought now, and seriously, that what the world needs most at present is a strict limitation on the excesses of technology and the renaissance and dissemination of certain poorly remembered spiritual and humanitarian values. Man might then conceivably become more worthy of his continued existence on this sorely tried planet.

Once again, and with feeling, we might recall the hymn written by Clifford Bax so soon after the ending of the first world war:

> Turn back, O man, forswear thy foolish ways.
> Old now is earth, and none may count her days;
> Yet thou, her child, whose head is crowned with flame,
> Still wilt not hear thine inner God proclaim —
> "Turn back, O man, forswear thy foolish ways."
>
> Earth might be fair and all men glad and wise.
> Age after age their tragic empires rise,
> Built while they dream, and in that dreaming weep;
> Would man but wake from out his haunted sleep,
> Earth might be fair and all men glad and wise.

Earth shall be fair, and all her people one;
Nor till that hour shall God's whole will be done.
Now, even now, once more from earth to sky,
Peals forth in joy man's old undaunted cry —
"Earth shall be fair and all her folk be one!"

MASSACHUSETTS TO PROVIDE BLOOD AND BLOOD DERIVATIVES

ELSEWHERE in this issue of the *Journal* the Massachusetts Department of Public Health announces the initiation within the next few months of a civilian blood and blood-derivatives program. An attempt will be made to furnish the citizens of Massachusetts with blood plasma and other blood products without cost, on the same basis as antiserums and vaccines. There is no doubt that such a program will be of the greatest value, and like undertakings have already been started in other parts of the country. A similar purpose is being accomplished in certain localities by the encouragement of blood banks in general hospitals or in institutions under the supervision of local or state health departments. Such blood banks, however, are not, as a rule, able to process the many fractions of human blood that are now called for by the clinicians. Proper authorities should have some control over these blood banks to ensure adequate provisions for sterility and a personnel trained in blood grouping and processing. It is also important to make provisions for preventing the transfer of disease by means of transfusions. Syphilis, malaria and homologous serum jaundice (infectious jaundice) are among the diseases that may be transferred, and under certain conditions, sensitization to various allergens may be transmitted.

The methods of processing blood derivatives have progressed to a point where large-scale production has become feasible and has already been put into effect. In a large measure, this has been due to the splendid accomplishments of workers at the Harvard Medical School under the guidance of Dr. Edwin J. Cohn and by their many collaborators throughout the country. The Red Cross has also worked out practical methods of large-scale collections of blood to supply the processing plants. No doubt the continuation of a program such as the one contemplated by the department will permit all these workers, as well as those in the Division of Biological Laboratories, to continue the development of blood derivatives and to study their uses and applications. Plasma, albumin, immune globulin, fibrin foam and other by-products have already proved useful in medicine and undoubtedly other valuable derivatives will eventually be devised.

A number of other factors are involved in any large-scale program for providing blood and its derivatives, and these must be satisfactorily disposed of before the plan can become well established and can reach a high state of efficiency. From the point of view of the general public, there is a good deal of spade work yet to be done to interest people to give blood now that the incentive of patriotism that served to bring donors to the Red Cross centers has been removed. A new approach and other publicity methods will be needed to assure the number of blood donations that are necessary to make a state-wide program workable. At present, some persons supply blood to hospitals because of their interest in the health and welfare of their relatives and friends, whereas others do it because of the financial reward.

There is also a need to inform the general practitioner about the values and use of the various blood fractions. Under the stimulus of war, plasma and other blood derivatives became readily available to the armed forces and were freely used. It is now recognized by most authorities that plasma is not an adequate substitute for whole blood but that it is useful as an emergency measure for the replacement of blood volume. Indeed, the continued use of plasma or plasma substitutes alone may be harmful in some cases, such as those of severe and prolonged sepsis and of blood loss. Furthermore, there may be a tendency for a physician to rely too much on the blood derivatives in certain types of conditions to the exclusion of adequate diagnosis and treatment of the underlying disease, which may be a severe infection requiring a specific anti-infective agent or a condition demanding surgery. The Massachusetts Department of Public Health, working in co-operation with the Massachusetts Medical Society, is preparing material for the education of the profession in the uses and abuses of the fractions of human blood.

Until such a time as the state program is prepared to supply whole blood or resuspended red cells throughout the Commonwealth, the public must be encouraged to continue to supply hospitals with sufficient donors to keep their blood banks solvent. With a wide community program, the relatives and friends of patients, who, in the past, have been largely responsible for the successful operation of these blood banks, may lose the urge to make blood donations. Even in the absence of such a program, the hospitals have had great difficulty in keeping their blood banks supplied. Furthermore, hospital patients are usually in greater need of whole blood than they are of plasma, as has been found in handling battle casualties.

The successful operation of a blood bank on a state-wide basis in Michigan for a period of more than two years has proved that it is possible to conduct such a project for the benefit of the public. The Massachusetts program, however, is more extensive in that it supplies not only plasma but also all the fractions of human blood. Such an ambitious program will dig deeply into the public purse. The Hyams Trust has made available to the department a building costing $176,000 for the processing of this blood, and the Legislature has appropriated $174,000 for the equipment and operation of the laboratory; but the maintenance of the program will require appreciable annual appropriations by the Legislature. There is no question that such an investment for the residents of Massachusetts is worth while, but the success of the venture demands the co-operation of physicians and the public — the latter both as taxpayers and as donors.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CIVILIAN BLOOD AND BLOOD-DERIVATIVES PROGRAM FOR MASSACHUSETTS

Within the next few months Massachusetts will offer its citizens a new and striking public-health service, when the Department of Public Health begins distribution of blood plasma and other blood products without cost on the same basis as serums and vaccines.

The experience of World War II has tremendously increased the knowledge of the uses of human blood and its derivatives. Among the outstanding of these developments is the separation of blood plasma into its various fractions, a process developed at the Harvard Medical School in close collaboration with the Division of Biologic Laboratories of the Department. The application of blood and its products in civilian medical practice will be greatly extended as a result of the increased knowledge that has been gained, and it is fortunate that the department can count on a large group of civic-minded persons who now know that they can contribute to the welfare of their fellow man through blood donations.

To make possible the statewide use of such a vital resource as human blood, the Department of Public Health has organized a program that will include the following: collection of blood donations as donor programs are organized by civic or other groups in various communities; processing of the blood to the various fractions of known value, such as plasma, albumin, gamma globulin, fibrin foam, fibrin film, blood grouping serums and other fractions still in the process of development, as well as resuspended red cells and whole blood as soon as suitable methods for their preservation are established; and distribution of these products through recognized channels and in accordance with community contribution of blood donations.

The program will operate as a unit of the Division of Biologic Laboratories. The Antitoxin and Vaccine Laboratory of this division celebrated the fiftieth anniversary of its foundation in December, 1944, and its fifty-first year promises to be one of large expansion. The Legislature has appropriated $174,000 to equip, staff and operate a blood and blood-derivatives program. The Godfrey M. Hyams Trust, of Boston, has donated $176,000 to Harvard University for the construction of a modern, well equipped laboratory building in which processing and fractionation of blood and its products can be carried out, as well as other essential procedures.

This program will provide for the citizens of Massachusetts a blood and blood-products service that will include all the advances developed during the war. These products are already known to be of unique value in the handling of cases of surgical shock and burns, in brain surgery and dentistry, in cases of anemia and hemophilic bleeding and in a variety of other surgical and medical emergencies. Some blood fractions are used in the control of measles and certain other infectious diseases. Provision of these products will thus represent one of the greatest steps in the promotion of health and the saving of life that the Department of Public Health has ever undertaken.

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR AUGUST, 1945

RÉSUMÉ

Diseases	August 1945	August 1944	Seven-Year Median
Anterior poliomyelitis	128	133	15
Chancroid	1	2	*
Chicken pox	121	192	121
Diphtheria	11	5	8

Dog bite	1008	1025	1064
Dysentery, bacillary	53	18	15
German measles	38	57	34
Gonorrhea	459	426	426
Granuloma inguinale	0	0	*
Lymphogranuloma venereum	1	0	*
Malaria	69	47	2
Measles	274	227	281
Meningitis, meningococcal	6	30	4
Meningitis, Pfeiffer-bacillus	1	3	1
Meningitis, pneumococcal	1	2	1†
Meningitis, staphylococcal	2	0	0†
Meningitis, streptococcal	0	0	0†
Meningitis, other forms	4	1	0†
Meningitis, undetermined	1	4	4†
Mumps	311	273	157
Pneumonia, lobar	93	72	77
Salmonella infections	48	24	13
Scarlet fever	157	197	195
Syphilis	293	393	367
Tuberculosis, pulmonary	215	232	265
Tuberculosis, other forms	12	13	24
Typhoid fever	4	5	9
Undulant fever	5	7	5
Whooping cough	531	261	429

*Made reportable December, 1943.

†Four-year average.

Comment

Anterior poliomyelitis cases for August markedly exceeded those for July but were slightly fewer than the number of cases in August of last year, which was 133. It appears that our experience with poliomyelitis this summer is similar to that of 1944.

The enteric diseases were prominent in August. Salmonella infections were reported more frequently than in any month since 1937. Bacillary dysentery, which increased from 1 case in June to 44 in July, still remained high. Typhoid fever, of which there were no cases in July, appeared on the scene again, though in number less than half the seven-year median.

Geographical Distribution of Certain Diseases

Actinomycosis was reported from: Falmouth, 1; total, 1.

Anterior poliomyelitis was reported from: Abington, 1; Acton, 1; Athol, 2; Barnstable, 1; Becket, 2; Belmont, 4; Beverly, 3; Boston, 25; Braintree, 1; Cambridge, 1; Chelsea, 2; Chicopee, 3; Concord, 1; Dedham, 2; Deerfield, 3; East Bridgewater, 1; Falmouth, 1; Gardner, 2; Gloucester, 8; Greenfield, 2; Hinsdale, 1; Holyoke, 3; Ipswich, 1; Lanesboro, 1; Lexington, 1; Malden, 8; Marblehead, 2; Medford, 2; Melrose, 2; Nahant, 1; Newton, 2; North Adams, 2; North Reading, 2; Norwood, 1; Orleans, 1; Peabody, 1; Pittsfield, 1; Quincy, 2; Reading, 2; Revere, 1; Salem, 1; Saugus, 1; Shirley, 1; Somerville, 3; Springfield, 4; Swampscott, 1; Wakefield, 1; Wales, 2; Wareham, 1; West Springfield, 1; Westboro, 1; Westfield, 1; Westwood, 2; Winthrop, 2; Woburn, 1; Wrentham, 1; Yarmouth, 1; total, 128.

Diphtheria was reported from: Boston, 3; Cambridge, 2; New Bedford, 1; Newburyport, 1; Norwood, 1; Reading, 1; Somerville, 1; West Bridgewater, 1; total, 11.

Dysentery, amebic, was reported from: Camp Edwards, 5; total, 5.

Dysentery, bacillary, was reported from: Amesbury, 1; Belmont, 3; Camp Edwards, 1; Foxboro, 1; Foxboro (State Hospital), 8; Framingham, 1; Peabody, 1; Pittsfield, 1; Waltham (W. E. Fernald School), 2; Worcester (state hospital), 35; total, 54.

Hookworm was reported from: Camp Edwards, 3; total, 3.

Lymphocytic choriomeningitis was reported from: Townsend, 1; total, 1.

Malaria was reported from: Andover, 1; Bedford, 1; Boston, 7; Brockton, 2; Camp Edwards, 42; Cushing General Hospital, 2; Haverhill, 1; Lawrence, 1; Newton, 1; Norwood, 1; Quincy, 2; Saugus, 2; Waltham (regional hospital), 3; Watertown, 1; Woburn, 1; Worcester, 1; total, 69.

Meningitis, meningococcal, was reported from: Boston, 3; East Bridgewater, 1; Southbridge, 1; Springfield, 1; total, 6.

Meningitis, Pfeiffer-bacillus, was reported from: Springfield, 1; total, 1.

Meningitis, pneumococcal, was reported from: Lawrence, 1; total, 1.

Meningitis, staphylococcal, was reported from: Attleboro, 2; total, 2.

Meningitis, other forms, was reported from: Boston, 3; Everett, 1; total, 4.

Meningitis, undetermined, was reported from: Braintree, 1; total, 1.

Salmonella infections were reported from: Amesbury, 1; Boston, 2; Cambridge, 2; Danvers (state hospital), 1; Lynn, 1; Malden, 1; Quincy (private school), 36; Saugus, 1; Stoneham, 1; Ware, 1; Weymouth, 1; total, 48.

Septic sore throat was reported from: Amesbury, 1; Boston, 7; Haverhill, 1; Lynn, 1; Merrimac, 6; Norwood, 1; total, 17.

Tetanus was reported from: Chicopee, 1; Worcester, 1; total, 2.

Trichinosis was reported from: Andover, 1; Boston, 1; Cambridge, 1; total, 3.

Typhoid fever was reported from: Chicopee, 3; Framingham, 1; total, 4.

Undulant fever was reported from: Deerfield, 1; East Brookfield, 1; Gloucester, 1; Somerville, 1; Whately, 1; total, 5.

CORRESPONDENCE

NATURE'S CORRECTIVE

To the Editor: Wars do not happen. Whether local or foreign, their cause is inadequate human thinking and behavior.

For years there has been abroad in the world the notion that somehow character, culture and contentment can come through the multiplication of machines. For several generations the selfish lust for comfort in excess of biologic needs and sanctions has led us to make more and more things faster and faster in order that life might become easier and easier. This had little regard for the ancient, unchanging and inflexible laws of Nature within which man must live if true progress is to be made. Like all animals man has limitations, — physical, mental and emotional, — which, when overstepped, invite Nature's intervention to restore her everlasting balances.

History shows and Nature knows that the character changes brought on by heedless easy living so poison human relations that, sooner or later, the resulting emotional conflicts spill youthful blood. And the reason why the war just ended was the greatest emotional explosion in history is that our sleepless machine-made devices, especially those used for the rapid interchange of indigestible ideas, have simultaneously deluded, frightened and embittered widespread populations.

Nature's methods are slow, adapted to man's limited abilities, and solicitous of the long-distance welfare of the species. Machine methods are swift — too swift for the sound evaluation and control of their many complex and often pathologic consequences, including corrupting concepts of "labor," "leisure," "security" and impulsive "planning."

Thus the picture contains more than the fantastic physical mass production of machines, with their domestic and foreign social, political and economic complications and repercussions. We have also mass production of frustrations, jealousies, dislocations, fears and follies and a vast train of unmanageable emotional and other distempers, which twice have blazed into world war. The common man, forsaking valuable ideas and goaded by his machine-made emotions and unbiologic illusions, resorts to violence — each nation according to real or fancied necessity. And once again Nature steps in to invoke her bleak rule governing survival of the fit.

When the excessive mechanization (including political and economic) of society creates such unnatural, swiftly changing and confused surroundings that distortion and deterioration of standards and values result, man's limited biologic equipment (including his mental, moral and spiritual potentialities) is unequal to the task of making rational peaceful adjustments. This seems to be a law of diminishing cultural returns.

The "Great Push Up" cannot work its magic, and the principles and practices of true Christian democracy are not likely to prevail, in societies shadowed by the astronomic complexities wrought by machine-made delusions and emotions, brewed in highly abnormal urbanized industrial economies.

Meanwhile we still live in an orderly world. Above the tumult, strife and sadness, Nature goes her just and appointed way. That some should perish is the price society must pay for venturing too fast, too far and too selfishly on new frontiers. Having misused our talents and liberties, Nature seeks through measured disciplines and purges to return man to simpler faiths and enterprises, better fitted to his understanding and control.

Finally, the unquenchable thirst of the human soul for freedom — physical, mental and spiritual — again moves men to recapture and reorient, according to their lights, those ideas and ideals under which they wish to live. Thus do men, serving Nature, strive to compose the increasingly emotional and unmanageable world that their imperfect powers have built.

A. E. P. Rockwell, M.D.

Shrewsbury, Massachusetts

DEPRIVATION OF LICENSE

To the Editor: At a meeting of the Board of Registration in Medicine held on September 12 the Board voted to revoke the registration of Dr. Abraham Freitag because of gross misconduct in the practice of his profession, as shown by his recent court conviction.

H. Quimby Gallupe, M.D., *Secretary*
Board of Registration in Medicine

State House
Boston

AN APPEAL

To the Editor: This is a copy of a letter that will appear this month in the *Hippocrat*, the official publication of the Hampden District Medical Society. Can anything be done about it?

To the Editor: To those of us who gripe about an income tax, to those of us who are so busy calling ourselves specialists that we cannot attend to night calls and general practice any more, to those of us who crab because so-called "lesser men" are getting all the business and to those of us who would momentarily forget that a hundred men from this area have not only risked their skins but have been working for about $100 a week for several years past while two hundred of us have been living in safety and comfort, I submit this copy of a letter that I received today from a very essential man who waived a disability and who is, and always has been, as humble in his medical career as he is competent.

After thirty-seven days at sea we finally landed here in the Philippines, living in tents in a large staging area with all its attendant discomforts — crowded tents, poor food, no cigarettes unless you buy them from the natives for $4.00 a carton and a half-mile walk to the nearest latrine and, to top it off, steaming heat alternating with torrential downpours. We are scheduled to stay here six weeks, and then on to Japan. Quite a future now that the war is over. You are acquainted with the red tape of the Army, and it may be a long time before any of us get home. There are many medical officers in the outfit who have spent eighteen to thirty-six months in the ETO. It is all so unfair, to them especially, since we know of many medics in the states who have never been overseas. As for myself, I fail to see what use I can be to the Army now that there are no more battle casualties, for which I thank God. While the war was on, I did not complain, for I knew that I had a job to do, but now I and countless others have plenty to gripe about. What little news we get from the states is too confusing to give us much hope; the wrangling between President Truman and the Senate regarding the soldiers makes us wonder whether the people at home realize what three or four years in the Army can do to a former civilized human being. You may recall that I was on the essential list at my hospital but asked them to release me, since I felt it my duty to join the Army. Now, after three years, I feel that I have made my contribution. It would make you sick to see the thousands of medical officers sitting around in these staging areas with nothing to do and no work for the near future, and yet the Army holds them despite the crying need for doctors at home.

I may as well come to the point. Is there anything you can do either through the Massachusetts Medical Society or by your own efforts to hasten release from this futile existence. Most of the doctors are working on their congressman and on Senator Mead, of New York, who apparently champions our cause. For the sake of old times, I should eternally appreciate anything you might accomplish to return me to the civilized type of living to which I am entitled. Remember me to the others, and my best to you and yours.

This particular doctor is the most competent man in his field in Western Massachusetts. He is a thorough gentleman and one of the finest men of my acquaintance. One can readily see that he is not politically minded, yet his heart must be in turmoil or he never would have committed himself to a letter such as this. Although some will suspect whence this letter comes, I shall refuse to divulge the name until such time as I may meet a sincere effort for his release. Incidentally he does not speak for himself alone.

W. A. R. Chapin

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Essentials of Allergy. By Leo H. Criep, M.D., assistant professor of medicine and lecturer in immunology, School of Medicine, University of Pittsburgh, chairman, Department of Medicine, Montefiore Hospital, member of senior staff in medicine, Presbyterian and Passavant hospitals, Pittsburgh, and consultant in allergy to the Medical Service, United States Veterans Administration. With a foreword by Robert A. Cooke, M.D., chairman, Committee on Education, American Academy of Allergy. 12°, cloth, 381 pp., with 42 illustrations and 1 plate. Philadelphia: J. B. Lippincott Company, 1945. $5.00.

This manual is intended for the use of the medical student and the practising physician. The subject matter is dealt with in outline form, resulting in conciseness and clarity of expression. The work is made up of two parts; the first deals with the basic immunologic principles of anaphylaxis and allergy, and the second, comprising most of the text, discusses the diagnosis and treatment of allergy and the various allergy entities. The manual concludes with chapters on the diagnostic skin tests and on allergy in children. Case reports are appended to each chapter to illustrate essential practical considerations. In controversial issues the view that is most readily acceptable is adopted for teaching purposes. The printing is good, on good paper, with a good type. There is an adequate index, and selected bibliographies are appended to each chapter. The manual should prove useful within its intended scope.

Patients Have Families. By Henry B. Richardson, M.D., associate professor of clinical medicine, Cornell University Medical College, attending physician, New York Hospital, and visiting physician, Bellevue Hospital. 8°, cloth, 408 pp., New York: The Commonwealth Fund, 1945. $3.00.

Physicians are beginning to realize that patients cannot be considered apart from their families and their communities. Their illnesses may be profoundly affected by the stresses and strains of these human relations. This book is based in large part on a family study conducted by a number of New York organizations seeking a better understanding of the family as a unit in medical care and of the implications for treatment. Dr. Richardson tells in nontechnical language of characteristic family patterns that appear in connection with different illnesses, and indicates their significance to the physician in diagnosis and treatment. He demonstrates the advantages of pooling the different services of the hospital and of the community to get a complete picture of the family, and shows how such co-operation can improve medical practice. The book should be in all medical, hospital and social libraries and should be of importance to all physicians and to others who are interested in family and social welfare.

(*Notices on page xix*)